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Original Communications

NEUROGENIC TUMORS OF THE SYMPATHETIC NERVOUS SYSTEM IN CHILDREN

REPORT OF THREE CASES SURVIVING FOR A YEAR OR LONGER

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MALIGNANT tumors in the region of the adrenal glands are not uncommon in children. The majority of such tumors are composed of embryologically young cells, derived from the sympathetic nervous system, which metastasize so readily as to be almost invariably fatal. To these neoplasms the terms of neurocytoma, neuroblastoma, sympathogonioma, and sympathicoblastoma have been applied. Less common are ganglioneuromas, tumors of similar origin but more highly differentiated. The latter may arise, as do the former, from the adrenal medulla or from the ganglia of the sympathetic chain, and consequently may be encountered in a variety of sites usually close to the dorsal midline. Ganglioneuromas grow slowly and cause symptoms chiefly through occupancy of space and pressure upon neighboring structures. Occasionally they extend through intervertebral foramina into the spinal canal and give rise to symptoms and signs of compression of the cord. Scant attention has been paid in pediatric literature to the more benign tumors of this group in which recognition and surgical extirpation offer extremely favorable prognosis. In this report we wish to record two instances in which children have survived a year or more after the discovery of ganglioneuromas, and to cite one instance in which after the discovery of an abdominal sympathicoblastoma the patient has survived for six years.

CASE REPORTS

CASE 1.—M.F., an Italian female, was born on Oct. 5, 1931, at the Fifth Avenue Hospital. From the age of four months she suffered from anorexia, irritability, and gastrointestinal disturbances which resulted in a failure to gain weight. At 7 months weakness of the right leg was noted, and she was admitted to the Willard Parker

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Hospital on May 29, 1932, with a tentative diagnosis of acute anterior poliomyelitis. Examination at this time showed flaccid paralysis of the right leg with weakness of the left. The knee jerks could not be elicited, and all the deep tendon reflexes were diminished. Abdominal reflexes were present. The spine was straight and somewhat rigid in the lumbar region. Lumbar puncture was performed, but no fluid could be obtained. During the ensuing week remittent fever developed which ranged between 100° and 105° F. Weakness of the left leg progressed to flaccid paralysis and was followed by paralysis of the lower abdominal wall, loss of superficial abdominal reflexes and development of an area of anesthesia which extended from below the costal margin to the toes on each side. She also lost the power of micturition and defecation. Roentgenograms of the spine revealed no abnormalities. Two more lumbar punctures were attempted without success but a cisternal tap yielded clear fluid under increased pressure with normal chemical and cytologic content.

On subsequent examination a smooth, firm mass was palpated in the left upper abdominal quadrant extending posteriorly. From the mass no pus was obtained by aspiration. A barium enema disclosed anterior and downward displacement of the splenic flexure of the colon by a mass which compressed it from without. Intravenous pyelography was not wholly satisfactory, but the left kidney seemed to be enlarged and displaced downward.

On June 14, 1932, the left renal region was explored under local anesthesia and a soft, red, friable tumor was encountered extending out from the psoas muscle and fascia retroperitoneally. The mass was broken during extirpation and a small portion of its capsule remained in situ. The surgeon thought that the neoplasm was a sarcoma arising from and attached to the lateral edge of the lumbar spine. No definite extension into the intervertebral foramina was described. Microscopic sections of the tumor (Fig. 1) showed irregular nests of cells rather closely packed and separated by a fine fibrillar stroma. The cells were dark staining, small round cells with definite nucleoli and scanty cytoplasm. Occasionally a cell having the morphology of a small ganglion cell could be identified. There were many areas of necrosis and hemorrhage. A diagnosis of neurocytoma of the adrenal was made, with which Dr. Ewing concurred.

The child made a satisfactory recovery from the operation and, because of the grave prognosis, was referred to the Presbyterian Hospital for a course of deep x-ray therapy to the left renal region. During the following eight months she received a total radiation of 2400 r units. During this period no evidence of local or remote metastasis was uncovered through physical or roentgen examination. The neurologic status remained unchanged except for the progression of bilateral foot drop due to shortening of the tendo Achilles. Bladder paralysis persisted and she was admitted for a period to the Neurological Institute of New York because of pyuria. Physiotherapy and orthopedic correction of deformities of her feet were attempted with little success.

No essential change in her condition occurred during the three years following removal of the tumor. In August, 1935, she was admitted again to the Neurological Institute for more complete evaluation of her status. Flaccid paralysis of the lower extremities, bladder and rectal paralysis, and loss of all sensation below the 11th thoracic segment were still present. Several attempts were made to obtain satisfactory manometric spinal fluid determinations, but the results were inconclusive. On one such occasion yellow fluid under low pressure and with a high protein content raised the question of spinal subarachnoid block. Although opinions differed as to the etiology of her abnormal neurologic findings, it was generally agreed that an intrathecal neoplasm was more than a remote possibility. Because improvement

seemed impossible without surgical intervention, a laminectomy was performed on Oct. 10, 1935. The spines and laminae of the 9th to 12th thoracic vertebrae were removed. Beneath the arch of the 12th vertebra the dura was thickened, and the cauda equina was adherent to it. The nerve roots were inflamed in a localized area. No evidence of tumor tissue was encountered and no palliative surgical measures were possible. The child made a satisfactory recovery from the operation but showed no improvement. Subsequent physiotherapy effected no improvement in her musculature. She was still alive, though paralyzed, and showed no evidence of recurrence or metastasis six years after the removal of the tumor.

CASE 2.—R. W. was a Jewish girl 6½ years old, admitted to the Babies Hospital on Jan. 17, 1937. Except for the common contagious diseases she had never been ill. There was no constipation or urinary disturbance. Since the age of four she had had an intermittent, foul vaginal discharge, numerous smears of which had failed

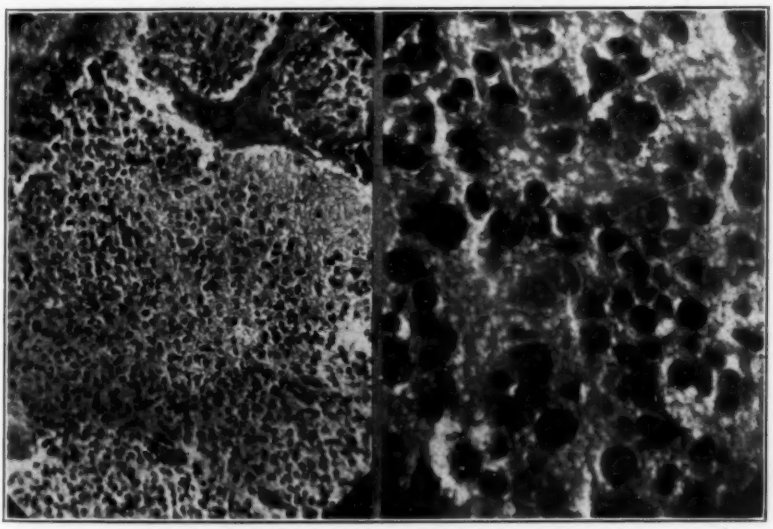

Fig. 1.—Case 1. Low and high power photomicrographs of tumor removed. Magnification 110× and 460×.

to reveal gonococci. One month before admission she entered the Willard Parker Hospital with a light attack of scarlet fever, and an abdominal mass was discovered on routine examination.

Physical examination at the time of admission to the Babies Hospital showed no significant findings except in the abdomen. She was well nourished and developed and not ill. A large, firm tumor was easily palpable in the left lower abdominal quadrant. It was about the size of a man's fist and firmly attached to the surrounding structures. The surface was slightly irregular and was not tender. It was readily palpable on rectal examination and filled the left side of the pelvis. A barium enema (Fig. 2) showed that the rectum and sigmoid were displaced to the right and considerably narrowed by the mass. The external genitals were normal with no discharge evident. Sexual precocity was not present, and follicular hormone could not be demonstrated in the urine. Roentgenograms of the chest and long bones revealed no metastases. Blood count, urinalysis, Mantoux test, Kahn reaction, vaginal smears,

and sedimentation rate of the red blood cells were all normal. Most of the consultants who saw the child felt that she had a tumor of, or associated with, the left ovary.

On Jan. 21, 1937, exploratory laparotomy was performed and a large solid tumor encountered which reached downward from the umbilicus and practically filled the pelvis. The tumor was vascular and lay retroperitoneally. The gross appearance suggested a malignant sarcoma, and the surgeon felt that operative removal was too hazardous to be justified. Biopsy was taken and the abdomen closed. The right

Fig. 2.—Case 2. Barium enema showing compression and rightward displacement of the rectum and sigmoid.

ovary was examined at operation and appeared normal; the left could not be seen. The patient made a prompt recovery from the operation.

From the tissue removed at operation a diagnosis of ganglioneuroma was made. Since exact diagnosis of the neoplasm improved the prognosis, an attempt at removal was deemed essential. A second operation was performed on March 16, 1937, and the entire tumor removed with some difficulty. During the procedure trauma to the posterior wall of the bladder was suspected. A copious ooze of thin, bloody discharge from the vagina followed operation and necessitated two transfusions. The pa-

tient's general condition improved, but she became incontinent of urine with constant dribbling. Cystoscopy revealed a vesicovaginal fistula and an indwelling mushroom catheter was inserted to prevent distention of the bladder. The ability to void was regained, the dribbling ceased, and the child was discharged two months after the second operation.

The tumor weighed 370 grams and had been removed in two parts. The larger mass measured 10 by 7 by 5 cm. and was ovoid in shape, with slightly rounded elevations. It was partially enclosed by a thin, fibrous capsule. The second mass was roughly dumbbell in shape and measured 13 by 6 by 2 cm. The tumor was firm except for one slightly fluctuant area. The cut surface was translucent and white with a faint brownish tint, and coarse, pale fibers formed an interlacing network or whorls. One small cyst contained blood. Microscopically the tumor was composed of bundles of nerve fibers cut longitudinally and tangentially. Between them were

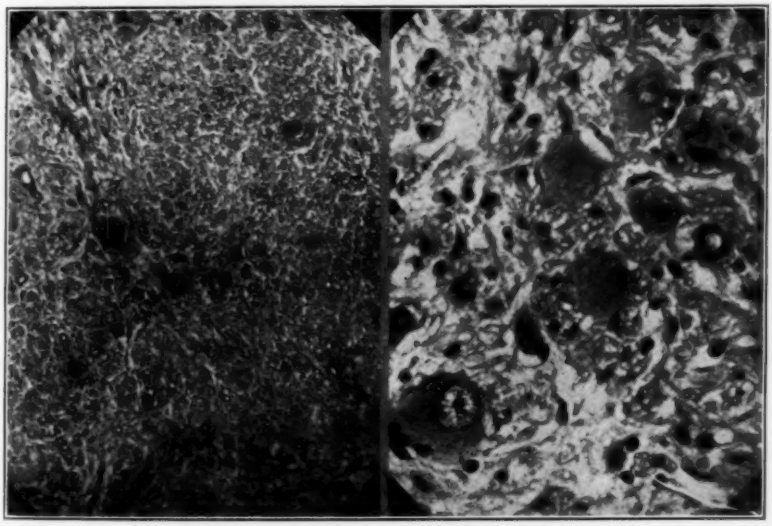

Fig. 3.—Case 2. Low and high power photomicrographs of the tumor removed. Magnification 110× and 460×.

scattered cells, singly or in nests, most of which were ganglion cells. These varied in size, some were greatly hypertrophied, and many contained two to four nuclei. In some, Nissl granules or lipochrome pigment could be identified. Numerous cells showed degenerative changes evidenced by swelling, vacuolization or hyalinization of the cytoplasm, and pyknosis or karyolysis of the nuclei. Axones were demonstrable in some areas. While the main portion of the tumor showed the picture just described, small regions were more cellular and the morphology of the tumor cells varied considerably. A few contained small, deeply stained nuclei without visible cytoplasm; in a greater number the nuclei were larger, round or oval, and vesicular, with distinct chromatin granules at the periphery. The cytoplasm ranged from scant to abundant and in the cell groups progressive stages of differentiation from sympathogonia to mature ganglion cells could be traced. In these cellular areas bundles of nerve fibers were lacking, but delicate eosinophilic fibrils were numerous between the cell bodies. Recent hemorrhage or pigment-laden phagocytes were present also in the regions of

greatest cellularity. About some of the blood vessels were accumulations of small round cells. The diagnosis of ganglioneuroma made from the biopsy specimen was confirmed (Fig. 3).

One year after operation the child was in excellent health, without evidence of recurrence or metastasis, and with good urinary control except for occasional nocturia.

CASE 3.—Y. S., a white girl aged 9 years, was admitted to the Babies Hospital on Feb. 2, 1937, as a private patient of Dr. Adrian V. Lambert. Her previous medical history was not remarkable, since she had not been ill except for measles, pertussis, and varicella. Three months before admission she contracted a cold followed by fever of 104° F., slight cough, and pain in the left chest. A diagnosis of bilateral pneumonia was made by her physician. Her temperature fell slowly by lysis over a period of nine days and then began to spike daily. Because of failure to improve she was admitted to the Mary Immaculate Hospital, Jamaica, in December, 1936.

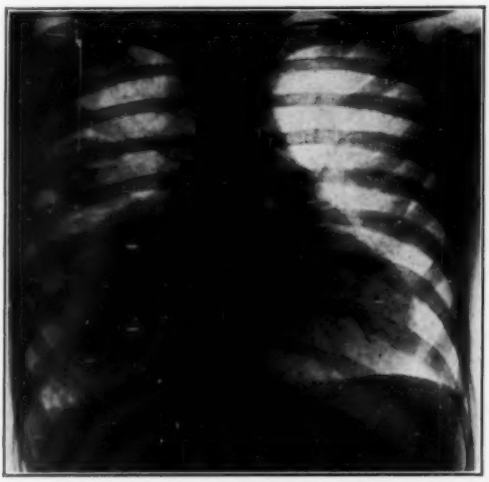

Fig. 4.—Case 3. Postero-anterior roentgenogram of the chest taken on Jan. 9, 1937, showing an abscess in the right upper lobe and dense tumor shadow at the right base.

Roentgenograms of the chest taken on Jan. 9, 1937 (Fig. 4) disclosed a circular dense shadow containing air and a fluid level in the lower portion of the right upper lobe. In addition there was a large dense shadow which extended downward and outward from the region of the right hilum to the diaphragm. The findings were interpreted as a lung abscess with an encapsulated empyema at the right base. Needle aspiration of the chest was performed and 20 c.c. of thick green pus were removed, from which pneumococci were cultured. On the following day a section of the right tenth rib was removed posteriorly and the pleura drained. No pus was encountered, the wound did not discharge, and yet her temperature continued to spike for two weeks. On Jan. 23 another roentgenogram (Fig. 5) showed almost complete clearing of the abscess cavity in the right upper lobe, but the shadow at the right base was somewhat larger and in the lateral view appeared to be bulging forward from the posterior chest wall. The patient was consequently referred to Dr. Lambert, who considered that an encapsulated empyema was present which had not been reached by the first operation.

At the time of admission to the Babies Hospital, the child's temperature was 100° F., pulse 100, and respirations 22. She appeared chronically ill but was fairly well nourished. There was limitation of the respiratory excursion of the right chest with an area of dullness posteriorly extending downward from the scapular spine to the base, where the percussion note was flat. Over this area the breath, voice, and whisper sounds were diminished, and tactile fremitus was absent. The anterior portion of the right lung was hyperresonant on percussion and many rhonchi were

Fig. 5.—Case 3. Postero-anterior and right lateral roentgenograms of the chest taken on Jan. 23, 1937, which show clearing of the lung abscess in the right upper lobe and an increase in the size of the tumor shadow at the right base. In the lateral view the shadow presents a sharp convex edge bulging forward from the posterior chest wall.

audible. The left lung was clear, and there was no deviation of the mediastinal structures. A careful neurologic examination failed to disclose any abnormal findings.

On Feb. 3, 1937, a thoracotomy was performed. Sections of the 8th, 9th, and 10th ribs were removed posteriorly, and a solid, extrapleural tumor was encountered. This lay close to the spine and did not invade the pleural cavity. Its limits could not be well defined through the exposure. A tentative diagnosis of sarcoma was made and tissue was removed for microscopic examination. The patient made a satisfactory recovery and was sent home ten days after operation. She was alive and quite well a year later, and removal of the tumor is planned when her general condition warrants an extensive operative procedure.

The surgical specimen consisted of three round or irregular masses of grayish yellow, moderately firm, semitranslucent tissue. The largest mass measured 5 by 4 by 2 cm. The cut surfaces were pale yellowish gray and in one of the fragments tiny

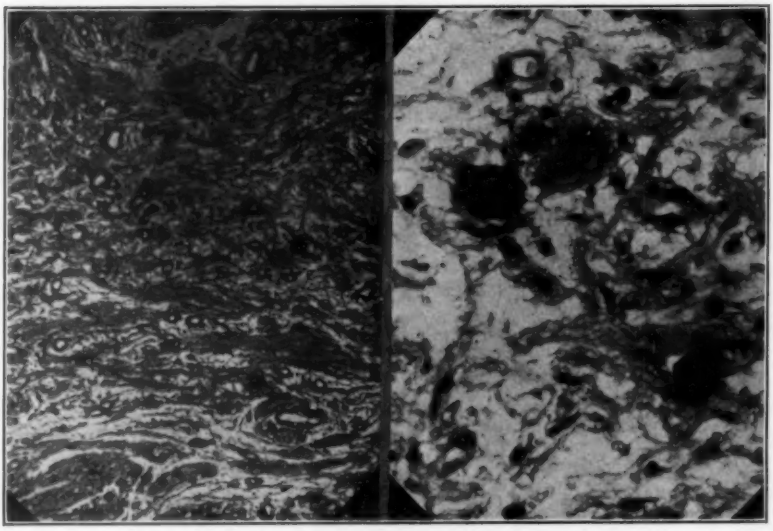

Fig. 6.—Case 3. Low and high power photomicrographs of tissue removed at operation. Magnification 110× and 460×.

hemorrhages were present. A small, red, soft lymph gland accompanied the tumor. Microscopically the tumor was made up of bundles of nerve fibers cut longitudinally and tangentially. Among them were scattered large ganglion cells most of which contained a single nucleus, though two or more nuclei in a cell were not uncommon. The cytoplasm of many of the ganglion cells was vacuolated and the nuclei were pyknotic. The stroma was edematous and relatively avascular. Small numbers of lymphocytes and plasma cells, often with a perivascular distribution, infiltrated the tumor. The diagnosis of ganglioneuroma was made. No evidence of tumor was found in the lymph node (Fig. 6).

DISCUSSION

The difficulty of making an accurate clinical diagnosis of these neurogenic tumors is apparent from the preceding case reports, for in each instance a faulty diagnosis was entertained until the true nature of the

tumor was established by microscopic examination of tissue removed from it. In Case 2 an ovarian cyst or tumor was suspected, and at operation the neoplasm discovered was regarded as a retroperitoneal sarcoma. In Case 3 the diagnosis was encapsulated empyema before, and mediastinal sarcoma after operation. In Case 1 the tentative diagnoses were first acute anterior poliomyelitis and later sarcoma. Conclusive proof of the sequence of morbid events in this patient is lacking, but in retrospect we believe the original diagnosis of poliomyelitis is untenable. The most reasonable reconstruction we can offer is that the abdominal tumor had extended through intervertebral foramina into the spinal canal and had compressed the roots of the cauda equina. The assumption of a compressing tumor at this site would account for paralysis of the lower extremities, for the sensory loss, for the persistent bladder paralysis, and for the evidence of spinal subarachnoid block. To complete the picture, we must assume that the remnant of neoplastic tissue left behind at operation was completely destroyed by deep x-ray therapy, leaving only the adhesions disclosed at laminectomy several years later.

It is well known that the malignancy of these neurogenic tumors is dependent upon the degree of differentiation of the cells in the individual neoplasm. Those which are composed of undifferentiated or incompletely differentiated cells are malignant. They may invade and metastasize widely, and are usually radiosensitive. Those composed of completely differentiated tissues are benign and are not affected by radiation. Between the two extremes of malignant and benign tumors are intermediate types and mixed forms which contain both well differentiated and undifferentiated or incompletely differentiated components. From the latter, metastases may arise. Within recent years several authors (Bigler and Hoyne[1]; Scott, Oliver, and Oliver[2]; Blacklock[3]; and Stern and Newns[4]) have discussed the histogenesis of the cells found in the various types of neurogenic neoplasms of the sympathetic system and have recommended classifications which are based on the stages of differentiation of the tumor cells. It is not within the scope of this brief report to review the several classifications advocated. For the malignant tumors of this group we have used the terms neurocytoma, neuroblastoma, and sympathicoblastoma as synonyms since all are established by wide usage.

In Case 1 the histologic picture was that of sympathicoblastoma which showed only slight tendency toward differentiation as evidenced by occasional small ganglion cells. Because of its nature, radiation of the residual tumor left at operation was advised, and, if our theory of intraspinal invasion is correct, the neoplastic remnant was destroyed. Survival of patients in whom sympathicoblastomas have been discovered is rarely seen, though Askin and Geschickter[5] cite Lehman's patient who was reported well fifteen years after the excision of a neoplasm which was a typical neuroblastoma pathologically. The possibility that these

tumors may undergo metamorphosis from embryonal to differentiated forms as the age of the patient increases is suggested by the extraordinary case of Cushing and Wolbach.[6] In this instance a tumor, histologically a neurocytoma, was removed from the subcutaneous tissue over the dorsal spine of a boy. Several years later the child developed symptoms of compression of the spinal cord and laminectomy was performed at the level of the original tumor. The intraspinal mass removed proved to be a well differentiated ganglioneuroma.

In our Case 2 the greater part of the tumor was made up of ganglion cells and nerve fibers, but in small areas sympathogonia and numerous sympathoblasts were intermingled with mature nerve cells. Since foci of indifferent cells are said to be present usually in ganglioneuromas, these regions undoubtedly represent sites of active growth rather than evidence of a mixed type of neoplasm. The absence of recurrence and metastasis add additional support to the benign character of the tumor. Even in patients with the mixed form of neurogenic tumor, the prognosis is not hopeless as demonstrated in a case reported from this hospital in 1928 by Wollstein.[7] In this instance a tumor of the adrenal region was removed from an infant 15 months old. The microscopic diagnosis was ganglioneuroma and sympathicoblastoma. At the time of publication of Wollstein's paper the child had survived for seventeen months. Radiation therapy had been given. We have been able to trace this child further and know that he was alive and well at the age of 12 years, i.e., eleven years after operation.

In our Case 3 the histologic picture was that of a benign growth, and complete recovery may be expected if the tumor can be removed in toto.

Of interest in connection with our first case and that reported by Cushing and Wolbach are the instances of proved invasion of the spinal canal by ganglioneuromas (Anitschkow,[8] Stout,[9] and Eloesser[10]). Similar invasion is probable, though unproved, in other patients with ganglioneuromas and symptoms of cord compression (Bland-Sutton,[11] and Hart and Ellison[12]). Hence the possibility of intraspinal invasion by neurogenic tumors should be recognized when neurologic signs accompany a demonstrable mass in thorax or abdomen.

As indicated above, treatment of differentiated neurogenic tumors is complete surgical extirpation. With the forms composed of embryonic cells, surgical removal should be supplemented by intense radiation.

SUMMARY

Case reports of three children who are alive with no evidence of recurrence or metastasis a year or more after the discovery of neurogenic tumors of the sympathetic nervous system are recorded.

One patient is living six years after removal of a sympathicoblastoma but retains her original signs and symptoms of compression of the

spinal cord. One patient is well one year after the removal of a large pelvic ganglioneuroma. One patient is well one year after the discovery of a thoracic ganglioneuroma which has not been completely excised.

The importance of accurate diagnosis of ganglioneuroma lies in the excellent prognosis following complete removal.

Surgical removal of sympathicoblastomas followed by radiation therapy may occasionally be effective in preventing recurrence or metastasis.

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BLOOD PRESSURE DETERMINATION IN CHILDREN

The Effect of the Width of the Cuff

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OUR attention was drawn to this subject by the frequency with which we found systolic blood pressure readings in 1- and 2-year-old children to exceed, by 10 to 20 mm. Hg, the standard of 92 mm. Hg established for children as old as 5 years by Faber and James[1] and Judson and Nicholson.[2] We believe this discrepancy to have been caused by our use of a narrow cuff, 5 cm. wide, such as is customarily used for infants and small children. It is well known that with adults, narrow cuffs give high readings[3-7] even when the subjects' arms are small. The importance of this fact has not been sufficiently appreciated by pediatricians. It is the purpose of this paper to show the extent of the change in systolic blood pressure readings caused by a change in cuff width, and the effect, in turn, of the circumference of the arm upon such changes.

LITERATURE

Faber and James[1] and Judson and Nicholson[2] report a large number of blood pressure determinations on children. They used cuffs 7, 9, 11, and 13 cm. wide, according to the size of the child. Others[8-17] working with infants as well as children, followed a similar custom, and for infants used cuffs from 4 to 7 cm. wide. None of these authors, however, presents any figures to show the extent of the differences in readings introduced by this wide range of cuff widths. That such differences may be important is suggested by the fact mentioned above, that with adults, narrow cuffs give too high readings. Müller and Blauel,[5] for instance, state that a cuff 4.5 cm. wide may give a reading 40 per cent higher than a 13 cm. cuff, and even in a man with thin arms accompanying an emaciated state, the difference was 19 per cent. A 13 cm. cuff is the standard for adults, regardless of the circumference of the arm. The use of this wide cuff for all adults, large and small, is justified, according to the fundamental work of von Recklinghausen[3, 4] and Erlanger.[6] The most important part of their evidence is this: when one takes the blood pressure with cuffs of different widths, it is found that although narrow cuffs give high readings, further increases in width beyond 12 to 13 cm. do not cause further significant decreases in readings. More consistent readings are therefore obtained with wide cuffs. Direct evidence that such wide cuffs also give

From the Normal Child Development Study of the Department of Diseases of Children, Columbia University, and the Babies Hospital.

readings close to the true intra-arterial pressure has been obtained by the comparison of the results obtained in one arm with the standard cuff and in the other with an intra-arterial cannula connected to a recording device (Müller and Blauel[5] and Hamilton, Woodbury, and Harper[18]). Further evidence that the soft parts of the arms play a minor role is presented by Janeway,[19] who found the same pressure in the two arms of a patient with one paralyzed arm and the other arm very well developed. Likewise Phipps[20] found that artificially increasing the circumference of the arm by wrapping meat around it did not change the reading obtained. Hensen[21] argues that the differences in the pressures found in arms and legs, and in adults and children would be greater if the soft parts were much of a factor.

These workers then in brief conclude that the size of the arm is not important, but the width of the cuff is, and they recommend a wide cuff.

Some authors differ from these views. Hering[22] found that the larger arm in asymmetrical subjects gave higher readings than the smaller arm. Straub and Kroetz[7] and Sahli[23] believe that a wide cuff dissipates the energy of the pulse and gives too low a reading. Recently, also, Woodbury, Robinow, and Hamilton[24] have stated that in the case of newborn infants, a very narrow cuff, only 2½ cm. wide, is correct. They base their opinion on the figures obtained with an intra-arterial cannula inserted in the umbilical artery, and connected with a photographic recording device, which is accurate to 1 mm. Hg. Their cuff determinations for comparison were made, however, not by auscultation, but by palpation at the wrist. They state that "the conventional cuff of pediatricians gave systolic readings 20 to 25 mm. Hg too low."

The literature thus presents certain inconsistencies. The problem still remains to determine the nature and extent of the changes in systolic readings introduced by changes in cuff width, and the relation of these changes to the size of the arm in different children and adults. The problem is important because the pediatrician is forced to use a narrow cuff when the subject's arm is short.

METHOD

In this study, a variety of cuff widths was employed in observations of the systolic pressure of subjects whose ages and arm circumferences varied widely. Diastolic pressures were found to be too variable to permit of analysis. The usual auscultatory technique was employed. The cuff, described in detail below, was wrapped snugly about the arm above the elbow. A mercury manometer was used, and the bell of the stethoscope was applied over the artery at the bend of the elbow. The criterion for systolic pressure was the occurrence of the first audible beat as the pressure in the cuff was lowered at the approximate rate of 2 mm. Hg every 2 seconds. In order to reduce the

error introduced by fluctuations in arterial pressure occurring from minute to minute, comparisons between two cuffs were always made at the same time, with one cuff on one arm and one of a different width on the other. Usually there were two observers, one at each arm. Occasionally there was only one observer. By using two cuffs connected to the same air system, a single observer could make approximately simultaneous observations. No readings were accepted until the subject had been quiet long enough for his blood pressure to become relatively constant. In spite of this, an error was still present because of the fact that for a period varying from minutes to

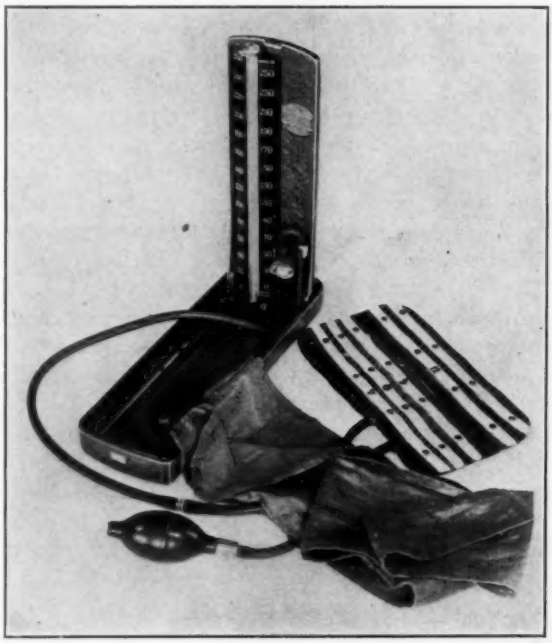

Fig. 1.—The variable width cuff opened wide for use with adults. For convenience, the seam on one side and the end of the silk outer bag has been opened.

hours, any given subject may have a difference in pressure in his two arms.[25] The standard deviation for the observations with a 5 cm. cuff was 3.25, and for a 13 cm. cuff it was 2.6. These figures were calculated from the average variance of multiple observations on twenty subjects.

It was found convenient to use a cuff which was adjustable in width. This cuff may be described as follows:

Five strips of tire patching rubber are cut 1 cm. wide and the same length as the rubber bag of an ordinary cuff. Four dress snaps are sewed to each of these. The strips are then cemented to the bag as shown in the photographs (Figs. 1 and 2).

The silk outer bag should be opened along the seam of one side and the end.

The use of the cuff is clearly shown in the photographs (Figs. 1 and 2). It can be seen that the cuff width is changed by folding the rubber bag within the silk outer bag. The fold itself does not introduce any change in the resultant readings other than that caused by the change in width.

RESULTS

Observations were made on 41 individuals who were well scattered over the age period of from 4 months to adulthood. Their arms varied in circumference from 12.5 to 32 cm. One hundred and ninety pairs

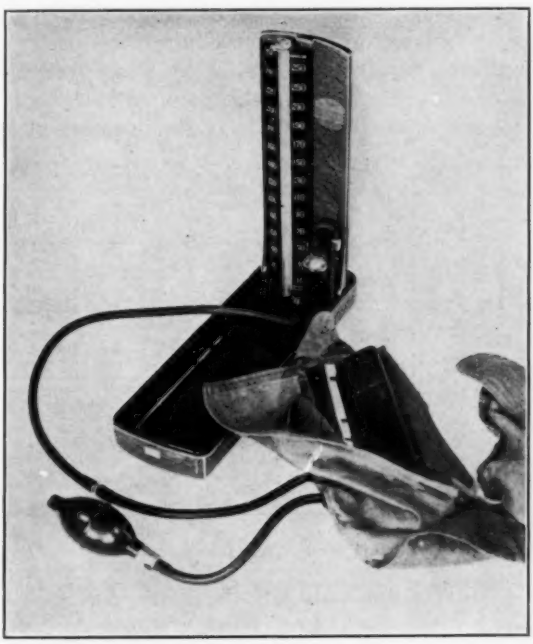

Fig. 2.—The variable width cuff folded and partially inserted in the silk outer bag, preparatory to use on a child.

of observations with a 5 and a 13 cm. cuff (the standard infant's and adult's sizes) gave an average reading 19.4 mm. Hg higher for the 5 cm. cuff. The range was from 2 to 52 mm. Hg, and the standard deviation was 7.9. Seventy-nine pairs of observations with a 7 and 13 cm. cuff gave an average difference of 10.2 mm. Hg in favor of the narrower cuff with a standard deviation of 5.1, and a range of from -4 to 22.

Ninety-seven pairs of observations with a 9 and 13 cm. cuff gave an average difference of 7.7 mm. Hg, with a standard deviation of 4.6 and a range of 0 to 18.

Thirty observations were made with a 13 cm. cuff paired with one 17 to 20 cm. wide. Usually the wider one was 20 cm. wide. The average amount by which the reading with this very wide cuff was lower than the 13 cm. cuff was only 2.4 mm. Hg. The range was from −12 to +4.

These figures show that the change in reading caused by a change in cuff width is significant and is very variable.

The effect of the circumference of the arm on the change in reading produced by a change in cuff width is shown in Fig. 3 and in Table I. In the graph the difference in reading between a 5 and a 13 cm. cuff is plotted against the circumference of the arm. Each point represents the average of readings for each of the 41 subjects. Any tendency for small arms to give low differences is not definite enough to permit prediction of the effect of a change in cuff size on the reading, on the basis of arm circumference. In fact chi-square calculated from

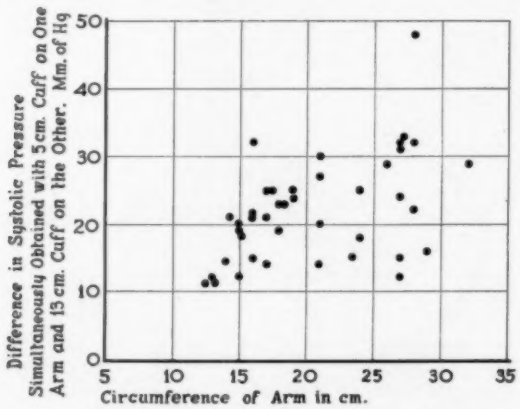

Fig. 3.—The relationship between the circumference of the arm, and the difference in systolic readings obtained simultaneously with a 5 cm. cuff on one arm and a 13 cm. cuff on the other.

TABLE I

A contingency table calculated from the data plotted in Fig. 3. Chi-square from this table = 2.968. Required for significance (P = 0.05): 3.841. There is no evidence that the observed distribution did not result from chance.

		NUMBER OF CASES WITH THE DIFFERENCE IN PRESSURE OBTAINED WITH A 5 AND A 13 CM. CUFF GREATER OR LESS THAN THE MEDIAN		
		LESS THAN THE MEDIAN	GREATER THAN THE MEDIAN	TOTAL
Circumference of Arm	Less than median	13	7	20
	Greater than median	8	13	21
	Total	21	20	41

Table I is 2.968, and to be significant it should be at least 3.841. From this, therefore, there is no evidence that the observed distribution is not the result of chance.

Of much greater importance are the results on individuals. For any given individual, the readings obtained with each of several cuff widths may be averaged, and then plotted against cuff width. Samples of such curves are shown in Figs. 4, 5, and 6. For comparison, a curve made from figures published by Erlanger[6] is shown at the top of Fig. 4. Most of the curves of the individuals in this study are similar, in that they show a flattening out in the part of the curve where wide cuffs are used. In individuals who show this type of curve, it is probably best, in the absence of information obtained from direct arterial cannulation, to follow the reasoning that has classically been applied to

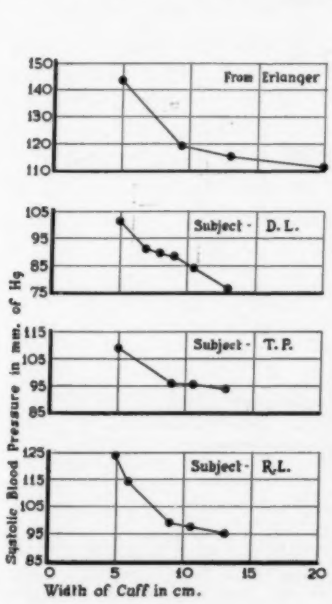

Fig. 4.

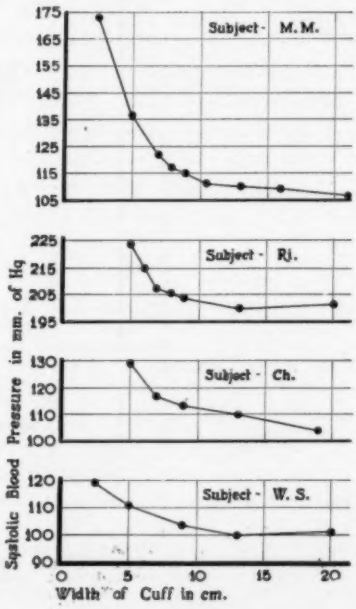

Fig. 5.

Fig. 4.—Systolic readings obtained with various widths of cuff on 4 normal individuals.
The first curve is drawn from figures published by Erlanger.[6] The subject was normal. Circumference of arm 30.5 cm.
Subject D. L., a 2½-year-old female, with arms 15.5 cm. in circumference.
Subject T. P., a 3-year-old male, with arms 16 cm. in circumference.
Subject R. L., a 1-year-old male. In this case the thigh was used. Circumference 22 cm.

Fig. 5.—The relationship between observed systolic readings and the width of the cuff in four individuals.
Subject M. M., a 26-year-old female. Circumference of arm 21 cm. Diagnosis: Normal.
Subject Ri., a 45-year-old male. Circumference of arm 21 cm. Diagnosis: Hypertension.
Subject Ch., a 29-year-old male. Circumference of arm 21 cm. Diagnosis: Duodenal ulcer.
Subject W. S., a 13-year-old male. Circumference of arm 13 cm. Diagnosis: Severe malnutrition.

adults. That is, one should select a cuff from the widths giving readings on the flat part of the curve, and for practical purposes this means the use of a cuff which is as wide as will fit the arm without impinging on the elbow or axilla.

However, certain subjects do not show this type of curve. These are illustrated in greater or less degree by D. L. in Fig. 4, and W. L. and D. H. in Fig. 6. In subjects like these who do not show a flattening out of the curve, there are no objective criteria by which the appropriate width of cuff can be selected.

In very young children and infants, usually under 6 months, it is frequently difficult or impossible to get consistent readings. This may be caused in part by lack of cooperation, and in part by the difficulty

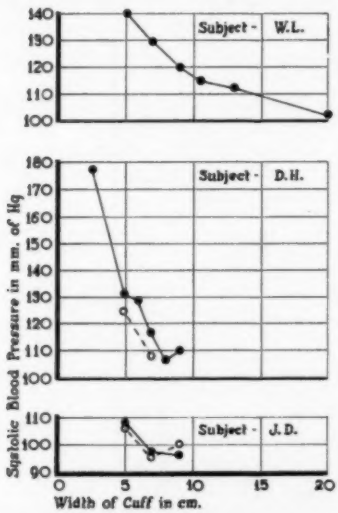

Fig. 6.—The relationship between observed systolic readings and the width of the cuff.
Subject W. L., a normal male, 32 years old, with an arm 32 cm. in circumference.
Subject D. H., a 10-month-old male. Circumference of arm 15 cm. Diagnosis: Acrodynia. Open circles show readings with patient asleep.
Subject J. D., a 19-month-old male. Diagnosis: Right hemihypertrophy. Circumference of right arm 17 cm., and of left arm 13 cm. The right arm is shown in solid dots, and the left arm by open circles.

of detecting, either by auscultation or palpation, the feeble pulse when it first begins to pass beyond the constricting cuff. The accurate method of Woodbury, Robinow, and Hamilton[24] would not seem to be applicable clinically. Blood pressure determination in this age group is at best uncertain.

SUMMARY

When one plots the readings for systolic pressure obtained with cuffs of different widths by the usual auscultatory methods against the cuff width, a curve is obtained which is characteristic for each individual.

In most cases, it rises sharply as one passes to successively narrower cuffs, and flattens out in the region of wide cuffs. This fact is the basis for the custom of using a wide cuff (13 cm. wide) for adults, regardless of the size of the arm. In the present report based on 41 individuals, the tendency for thin arms to cause a small increase in the reading with a narrow cuff (5 cm.), and large arms to cause a large increase was sufficiently slight so that it might have been caused by chance alone. It is therefore not wise to assume, as pediatricians have done, that the small arm of the child minimizes or eliminates the elevation in systolic reading caused by the narrow cuff which the shortness of the arm requires. Accordingly, if a single observation is to be made, a cuff as wide as will conveniently fit the arm should be used. To facilitate the use of a wide cuff, a variable width cuff was used, which is described.

Certain subjects do not show a flattening out of the curve in the region of wide cuffs. For such subjects, in the absence of information obtained from direct arterial cannulation, there are at present no criteria by which the width of cuff appropriate to the individual can be selected. Such subjects can be detected by the use of cuffs of several widths. This is facilitated by the variable width cuff.

Determinations in small infants are at best unreliable.

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A CONSIDERATION OF RACE AND SEX IN RELATION TO THE GROWTH AND DEVELOPMENT OF INFANTS

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MANY reports in the field of child health and growth fail to evaluate the relationship of race and sex to the development of the infant.* For example, some pediatric textbooks in general use in the United States, such as those by Grulee and Bonar (1926),[1] Holt and McIntosh (1936),[2] and Griffith and Mitchell (1937),[3] give birth weight standards for both sexes, or for different races, but fail to consider both race and sex in studying the growth and development of the infant. A few investigations, however, including one referred to by Baldwin (1921),[4] the ones cited by Robertson (1923),[5] and another made by Bakwin and Bakwin (1934),[6] take both race† and sex into account.

WEIGHT AT BIRTH

In an effort to obtain information with regard to the relationship of race and sex to the development of infants the birth weights of 2,923 infants born alive in the New Haven Hospital during the five-year period, 1928-32, were studied. Table I gives the number of these infants by race and sex.

TABLE I

NUMBER OF INFANTS BORN ALIVE AND WEIGHED AT BIRTH IN THE NEW HAVEN HOSPITAL, BY RACE AND SEX, 1928-1932

RACE	SEX		
	MALE	FEMALE	TOTAL
White	1,455	1,314	2,769
Negro	74	80	154
Total	1,529	1,394	2,923

As this table shows, considerably more white than negro infants were available for study and about the same number of males and females.

From the Children's Bureau, United States Department of Labor, with the cooperation of the Pediatric and Obstetric Departments of the New Haven Hospital and the Johns Hopkins Hospital. This study is part of a more comprehensive investigation of some of the factors that influence the health, growth, and development of the infant during the neonatal period.

*Race and sex have been frequently taken into account in studying the growth and nutrition of children of school age; for example, in the studies of L. T. Royster (Arch. Ped. 53: 259-266); M. J. Herskovits (Amer. J. Phys. Anthrop. 7: 439-446); A. Hrdlička (Anthropological investigations on 1,000 white and colored children of both sexes, the inmates of the New York Juvenile Asylum. With additional notes on 100 colored children in the New York Colored Orphan Asylum. 86 pp. Wynkoop Hallenbeck Crawford Co. New York and Albany. 1899); B. T. Baldwin (University of Iowa Studies in Child Welfare. Vol. 1, 411 pp.); and Martha M. Eliot, et al. (J. Ped. 9: 355-376).

†In the investigations cited by Robertson, nationality, rather than race, was studied.

TABLE II

PERCENTAGE OF LIVE-BORN INFANTS WEIGHING AT BIRTH LESS THAN 2,500, 3,000, AND 3,500 GM., BY RACE AND SEX (NEW HAVEN HOSPITAL, 1928-1932)

BIRTH WEIGHT (IN GM.)	PERCENTAGE OF INFANTS			
	WHITE		NEGRO	
	MALE	FEMALE	MALE	FEMALE
Less than 2,500	6.1	6.2	8.1	13.8
Less than 3,000	18.1	24.5	39.2	47.5
Less than 3,500	53.0	62.0	68.9	83.8

Table II shows for white males, white females, negro males, and negro females, the percentage of infants whose birth weights were less than 2,500, less than 3,000, and less than 3,500 gm. For example, about

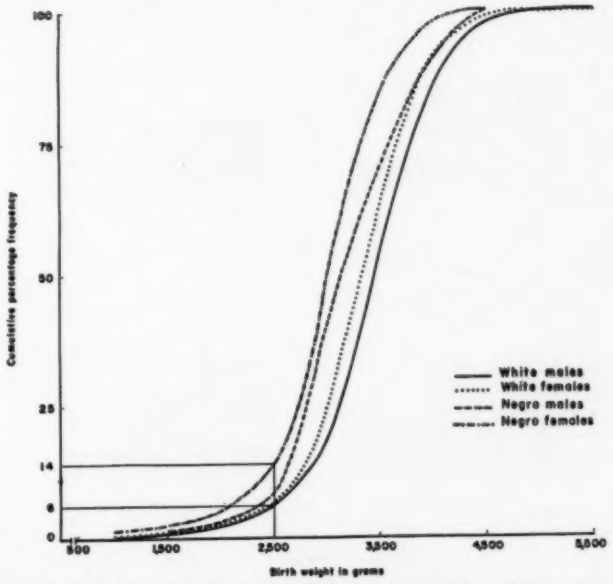

Chart 1.—Cumulative percentage frequency of the birth weights of live-born infants by race and sex (New Haven Hospital, 1928-1932).*

*Infants included in the study were divided as follows:
White males, 1,455 Negro males, 74
White females, 1,314 Negro females, 80

14 per cent of the negro female infants weighed less than 2,500 gm. at birth; 48 per cent, less than 3,000; and about 84 per cent, less than 3,500 gm.

Comparison of the percentages given in Table II shows that for both the white and the negro races a larger percentage of females than of males weighed less at birth than each stated amount and for each sex a larger percentage of negro than of white infants.

Race-sex differences in birth weight are shown also in Chart 1, on which curves have been plotted to show the percentage of infants of

each race-sex group weighing less than any given number of grams. These curves show, for example, that 50 per cent of the negro female infants weighed less than 3,003 gm.; 50 per cent of the negro males, less than 3,182 gm.; while for the white infants, the corresponding weights were 3,340 and 3,457 gm. In other words, the white infants weighed more on the average than the negro infants, and for each race group the average male infant weighed more than the female.

On this chart a vertical line has been erected at the point representing 2,500 gm. In addition, two horizontal lines have been drawn, one at the point where the vertical line intersects the curve for white

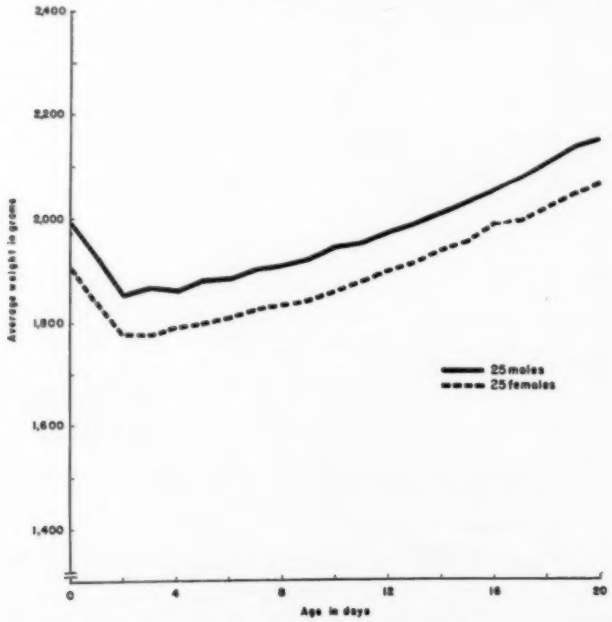

Chart 2.—Average daily weight of fifty premature negro infants, weighing less than 2,500 gm., observed from birth through 20 days of age in Johns Hopkins Hospital, 1936-1937.

males and the other where it intersects the curve for negro females. These two horizontal lines call attention to the fact that 6 per cent of the white male infants and 14 per cent of the negro females weighed less than 2,500 gm. This difference is of considerable interest in studying premature infants, for when a birth weight of 2,500 gm. or less is taken as a criterion of prematurity more than twice as many negro females as white males are included. In other words, this criterion assumes that relatively more negro infants are born prematurely than white. Is such an assumption justified?

GROWTH IN WEIGHT

The influence of sex on the growth and development of negro infants weighing less than 2,500 gm. at birth* has been studied for twenty-five male and twenty-five female infants born in the Johns Hopkins Hospital during 1936-37, who remained in the hospital twenty days or more and were weighed daily.† It should be noted that none of these infants suffered from any serious illness or nutritional disorder during the period of observation.

Chart 2 shows the average daily weight of the negro male and female infants for the first twenty days of life. Throughout this twenty-

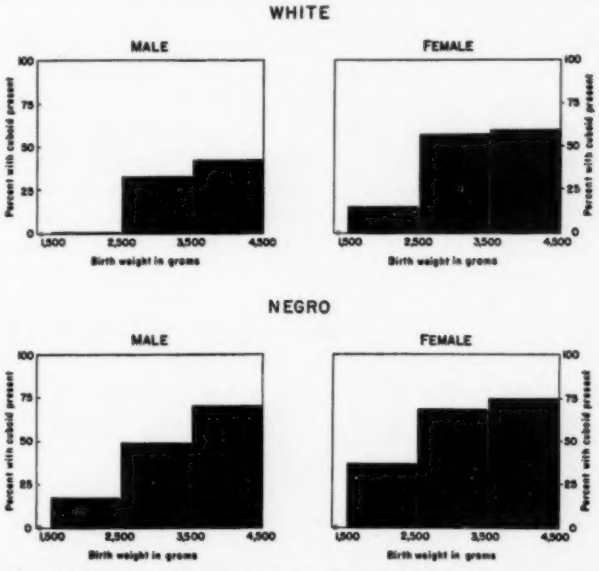

Chart 3.—Percentage of infants with cuboid present at birth by race, sex, and birth weight in Johns Hopkins Hospital, 1936-1937.*

*Number of Infants in Each Race, Sex, and Birth-Weight Group

Color	Sex	Birth weight in grams		
		1,500-2,499	2,500-3,499	3,500-4,499
White	male	13	64	46
	female	13	64	27
Negro	male	23	80	27
	female	30	99	12

day period the female infants as a rule weighed uniformly less than the males. In other words, the sex of the infant appears to influence his weight during the neonatal period.

*This problem will be studied also for a relatively more comparable group, for example, the infants whose birth weights form the lowest 10 per cent of the birth weights of all the infants of the same race and sex born alive in a given hospital during the same period.

†It was not possible to study the growth of white infants in the same way because very few who weighed less than 2,500 grams at birth remained in the hospital for as long as twenty days.

OSSEOUS DEVELOPMENT AT BIRTH

That the rate of osseous development also varies with sex and race was pointed out in 1925 by Alfred Hess and Weinstock,[7] but the influence of these two factors has not been recognized generally. Their importance is shown in a study of the presence or absence of the center for the cuboid, made at the Johns Hopkins Hospital in 1936-37. Roentgenograms of 498 infants, who were born in this hospital, were taken within seventy-two hours after birth. There were about the same number of these infants in each race-sex group (123 white males, 104 white females, 130 negro males, and 141 negro females). The results of this study are given in Chart 3.

The black columns (Chart 3) show the proportion of infants having the center for the cuboid present at birth, according to sex, race, and birth weight. The cuboid was present in the roentgenograms of infants weighing less than 2,500 gm., in the following proportions: 15 per cent of the white females, 17 per cent of the negro males, and 37 per cent of the negro females; it was absent from the roentgenograms of all the white males weighing less than 2,500 gm. In the group of infants weighing from 3,500 to 4,500 gm. at birth, the center was present in the roentgenograms of 42 per cent of the white males; 59 per cent of the white females; 70 per cent of the negro males; and 75 per cent of the negro females. In other words, the center for the cuboid is present more frequently in newborn negro infants than in newborn white infants of the same birth weight, and, within a given race group, it is present more frequently in the females than in the males. Thus, it may be seen that the development of the center for the cuboid also is related to both the race and sex of the infant.

CONCLUSION

These studies show that both race and sex should be taken into consideration in studying the growth and development of the infant.

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STUDIES IN THE USE OF CRYSTALLINE VITAMIN C (ASCORBIC ACID) IN THE PROPHYLAXIS AND TREATMENT OF INFANTILE SCURVY AND SOME OTHER DISORDERS OF INFANCY AND CHILDHOOD

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IN THIS report are recorded the results of studies on the use of crystalline vitamin C (ascorbic acid) in the prophylaxis and treatment of scurvy.

Following the identification of crystalline vitamin C in 1932 by both King and Waugh[1] and Svirbely and Szent-Györgyi,[2] this substance was first employed clinically in the treatment of adult scurvy by Schultzer[3] in 1933. In 1934 Svensgaard,[4] Neumann,[5] and Brugsch[6] employed ascorbic acid successfully in the treatment of infantile scurvy. The first report to appear in the American literature is that of Abt and Epstein[7] in 1935 wherein was recorded the cure of three scorbutic infants by means of oral therapy. Schultzer[3] in 1933 and Bauke[8] in 1934, as well as Goettsch[9] in 1935 demonstrated that ascorbic acid could be safely administered intravenously. Fisher and Leake[10] advised the observation of certain precautions, viz., the neutralization of the acid with sodium bicarbonate prior to subcutaneous or intramuscular injection, because of its irritating nature in the unneutralized state.

PROPHYLACTIC USE OF ASCORBIC ACID

The ready availability of the citrus fruits and other natural sources of vitamin C, such as tomato juice, in the United States will undoubtedly preclude the widespread use of ascorbic acid as an antiscorbutic in the dietary of the normal infant. However, in those countries where the citrus fruits are not readily obtained, ascorbic acid would seem to be a relatively inexpensive source of the vitamin. In addition, it would seem indicated in the dietary of the occasional infant who cannot tolerate citrus fruits. In the treatment of the scorbutic infant with diarrhea or vomiting, the parenteral administration of ascorbic acid furnishes a therapeutic agent of value. Some limited experience at the Children's Hospital with the use of ascorbic acid in the dietary of the premature infant, indicates that this substance is a well-tolerated source of the vitamin for such infants.

The comparative antiscorbutic efficacy of orange juice and ascorbic acid was studied in a group of nineteen white infants for a period of five months at the Children's Hospital of Philadelphia. Fourteen of

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the infants were kept on a large isolated ward for the entire period of the study. The remaining five were kept on a small isolated ward for two months, then discharged to the care of the Out-Patient Department. The feeding regimen of all infants was uniform. Milk with 5 per cent carbohydrate added was fed at a level of 55 calories per pound of expected body weight while cereals and strained vegetables were added when an infant attained the age of six months. Orange juice was fed to ten infants at a level of 2.5 c.c. per pound of body weight per day. Nine infants were fed 2.5 c.c. of an ascorbic acid solution per pound of body weight per day. The acid was dissolved in 10 per cent dark corn syrup, so that each 30 c.c. contained 10 mg. At the time the study was begun it was our impression that an ounce of orange juice (30 c.c.) contained 10 mg. of crystalline vitamin C. However, the analyses of Birch, Harris, and Ray,[11] and Kajdi[12] show that an ounce of orange juice contains approximately 20 mg. Consequently the infants given ascorbic acid solution received only half as much vitamin C as the infants given orange juice.

As far as we are aware, there have been no direct quantitative estimations of the daily vitamin C requirements of infants. Abbasy, Harris and co-workers,[13] calculating on a weight basis from values obtained for an adult, believe that 2.5 mg. daily meet the requirements of a 14 pound infant. Van Eekelen[14] has stated that a 70 kg. adult requires 60 mg. of ascorbic acid daily or about 0.84 mg. per kg., so that a 14 pound infant would require about 5.4 mg. The dosage employed in these studies was higher than either of these estimations, viz., 1.83 mg. per kg. of body weight, so that a 14 pound infant accordingly received 11.6 mg. daily.

Over the five-month period of observation roentgenograms of an arm and a leg, as well as physical examinations, were made at monthly intervals. During this period all the infants were free from clinical and x-ray signs of scurvy. In no instance were there any of the early radiologic signs of scurvy which Park and his associates[15] have pointed out. Whether or not these infants were saturated with the vitamin (i.e., had optimal stores) was not known since saturation tests were not done.

Recently Von Euler and co-workers[16] have reported the presence of an interesting dietary factor in orange juice and other fruit juices which they have termed the "J" factor. This factor has the property of preventing guinea pigs from developing pneumonia. He found that guinea pigs fed on a scorbutic diet developed scurvy but almost invariably died of pneumonia. Guinea pigs given orange juice supplements in which the vitamin C had been destroyed by oxidation developed severe fatal scurvy without manifestations of pneumonia. When crystalline vitamin C was added to the dietary as a supplement the pigs died from pneumonia but were protected from scurvy.

In view of these observations it is interesting to note that there was no significant difference between the two groups of infants in the present studies as far as the incidence, duration, or complications from respiratory tract infections were concerned.

THERAPEUTIC USE OF VITAMIN C

We have used ascorbic acid in the treatment of twenty-one infants with frank clinical scurvy. Table I summarizes the clinical findings on admission to the hospital in this group of infants.

The dosage of ascorbic acid employed in the treatment of these cases was varied to determine the response to different routes of administration. In most cases it was administered orally, the daily dose being dissolved in 5 or 10 c.c. of water and given at one time. When the acid was given intravenously, it was usually dissolved in 5 to 10 c.c. of normal saline solution. If the intravenous dose exceeded 100 mg., it was dissolved in hypotonic salt solution (half normal saline solution and half distilled water), using about 50 c.c. of this fluid. This is probably an unnecessary precaution, since the full dose may be administered in normal saline. Other than one infant, weighing 14 pounds who developed a hyperpnea of five minutes' duration following the intravenous administration of 1,000 mg. of ascorbic acid, there were no untoward local or constitutional reactions noted in the infants and children given the substance intravenously.

There are no precise data available concerning the amount of vitamin C necessary to produce a remission of clinical scurvy. It seems fair to assume that cure is under way when the common symptoms with which almost all of these infants were admitted, viz., pain and tenderness in the legs, have begun to recede. As Park and his coworkers[15] have pointed out, pain in the legs is the usual clinical manifestation of scurvy, appearing with "explosive suddenness" in infants who have had undoubted roentgenologic evidence of scurvy in their long bones for some time prior to the appearance of pain. While x-ray evidence of healing would seem to be more objective proof, most of the present cases were entirely free from symptoms at a time when roentgenograms of the bones gave no evidence of healing. Accordingly, in these cases the length of time for the "clinical" symptoms to disappear has been adopted as the time interval necessary for the initiation of healing. The amounts of vitamin C and the time intervals required to produce this degree of healing are listed in Table I. The amount of ascorbic acid utilized to effect clinical healing in these infants varied from 100 mg. to 500 mg. with an average of 310 mg.

For comparison there are listed in Table II the amounts of orange juice utilized to produce a similar degree of clinical improvement in a group of scorbutic infants treated solely with this agent. Assuming

TABLE I

SUMMARY OF CLINICAL DATA IN 21 SCORBUTIC INFANTS TREATED WITH ASCORBIC ACID

PATIENT'S CASE NO.	AGE (MO.)	COLOR	SEX	PERIOD OF VITAMIN C DEPRIVATION BEFORE ONSET OF SYMPTOMS (MO.)	DURATION OF ACUTE SYMPTOMS	CLINICAL FINDINGS ON ADMISSION								DOSE OF CEVITAMIC ACID EMPLOYED	TIME AT WHICH DEFINITE CLINICAL IMPROVEMENT WAS NOTED (DAYS)	TIME AT WHICH HEALING WAS NOTED IN THE X-RAY (DAYS)
						ANOREXIA	IRRITABILITY	TENDERNESS	SWOLLEN LIMBS	"SCORBUTIC" ROSARY	PETECHIAE	SWOLLEN (BLOOD) GUMS	FROG POSITION			
3686	6	W	M	6	10 days	+	+	+	0	+	0	0	+	50 mg. daily for 7 days — then 10 mg. daily (orally)	4	6
361249	8	B	F	8	2 mo.	+	+	+	+	+	0	+	+	50 mg. daily for 7 days — then 20 mg. daily (orally)	7	17
352535	8	W	M	8	1 mo.	+	+	+	0	+	+	+	+	50 mg. daily for 11 days—then 10 mg. daily (orally)	4	5
35730	8	W	F	8	10 days	+	+	+	0	+	0	+	+	50 mg. daily for 6 days — then 20 mg. daily (orally)	2	7
361858	9	B	M	9	14 days	+	+	+	0	+	0	0	+	50 mg. daily for 7 days — then 15 mg. daily (orally)	6	16
John H.	9	W	M	†—Given orange juice but vomited	21 days	+	+	+	+	+	0	0	+	50 mg. daily for 8 days orally)	2	8

TABLE I—CONT'D

37918	9	B	M	9	8 days	+	+	+	+	+	0	+	+	100 mg. daily (orally)	4	?
351856	9	W	F	6	1 mo.	+	+	+	0	+	+	+	+	50 mg. daily for 17 days (orally)	5	13
37808	10	W	M	4	21 days	+	+	+	0	+	0	+	+	100 mg. daily for 3 days (orally)	3	5
37569	10	W	M	10	21 days	0	+	+	0	+	0	0	+	100 mg. intravenously—then 100 mg. daily (orally)	5	15
35492	10	W	F	2½	1 mo.	+	+	+	+	+	+	+	+	100 mg. intravenously—then 50 mg. daily (orally)	5	9
361042	10	W	M	8		+	+	+	0	+	0	+	+	50 mg. for 7 days—then 15 mg. daily (orally)	6	?
351001	11	W	M	11		+	+	+	+	+	0	+	+	50 mg. daily for 7 days — then 20 mg. daily (orally)	7	9
35665	11	W	M	? (Had tomato juice sporadically)		+	+	+	+	+	+	+	+	50 mg. daily for 7 days — then 20 mg. daily (orally)	2	23
36362	11	W	M	11	21 days	+	+	+	0	+	+	+	+	50 mg. daily for 7 days — then 15 mg. daily (orally)	5	9

TABLE I—CONT'D

	PATIENT'S CASE NO.	AGE (MO.)	COLOR	SEX	PERIOD OF VITAMIN C DEPRIVATION BEFORE ONSET OF SYMPTOMS (MO.)	DURATION OF ACUTE SYMPTOMS	CLINICAL FINDINGS ON ADMISSION								DOSE OF CEVITAMIC ACID EMPLOYED	TIME AT WHICH DEFINITE CLINICAL IMPROVEMENT WAS NOTED (DAYS)	TIME AT WHICH HEALING WAS NOTED IN THE X-RAY (DAYS)
							ANOREXIA	IRRITABILITY	TENDERNESS	SWOLLEN LIMBS	"SCORBUTIC" ROSARY	PETECHIAE	SWOLLEN (BLOOD) GUMS	FROG POSITION			
	37555	12	W	M	9	7 days	+	+	+	+	+	0	+	+	300 mg. intravenously—then 100 mg. daily for 3 days (orally)	3	10
	35147	13	W	F	5	14 days	+	+	+	0	+	+	+	+	50 mg. daily for 3 days—then 30 mg. daily (orally)	10	13
	362112	13	W	M	7	3 days	+	+	+	+	+	0	+	+	50 mg. daily for 7 days—then 20 mg. daily (orally)	3	8
	371217	14	B	F	12	5 mo.	+	+	+	+	+	0	+	+	500 mg. intravenously (one dose)	4	11
Twins	371302	14	W	F	12	3 mo.	+	+	+	+	+	0	+	+	500 mg. intravenously (one dose)	2	18
Twins	371301	14	W	M	12	2 mo.	+	+	+	+	+	0	+	+	500 mg. intravenously (one dose)	3	18

TABLE II

SUMMARY OF CLINICAL DATA IN 13 SCORBUTIC INFANTS TREATED WITH ORANGE JUICE

PATIENT'S CASE NO.	AGE (MO.)	COLOR	SEX	PERIOD OF VITAMIN C DEPRIVATION (MO.)	DURATION OF ACUTE SYMPTOMS	CLINICAL FINDINGS ON ADMISSION								DOSE OF ORANGE JUICE EMPLOYED	TIME AT WHICH DEFINITE CLINICAL IMPROVEMENT WAS NOTED (DAYS)	TIME AT WHICH HEALING WAS NOTED IN X-RAY
						ANOREXIA	IRRITABILITY	TENDERNESS	SWOLLEN LIMBS	PETECHIAE	"SCORBUTIC" ROSARY	SWOLLEN (BLOOD) GUMS	FROG POSITION			
332628	7	W	F	6	1 mo.	+	+	+	0	0	+	0	+	6 ounces daily	9	
332764	8	W	F	8	3 days	+	+	+	0	+	+	+	+	6 ounces daily	9	
331464	9	B	F	?	1 mo.	+	+	+	0	0	+	0	+	4 ounces daily	6	
33466	9	W	M	9	7 days	+	+	+	0	0	+	0	+	4 ounces daily	7	
321288	9	W	F	8	21 days	+	+	+	+	0	+	+	+	6 ounces daily	5	
323652	7	W	F	7	1 mo.	+	+	+	+	+	+	+	+	6 ounces daily	2	
331492	10	W	F	10	2 days	+	+	+	0	0	+	+	+	4 ounces daily	10	
361781	8	W	F	8	2 days	+	+	+	0	+	+	+	+	4 ounces daily	4	No healing on 8th day
322358	10	W	F	10	10 days	+	+	+	+	0	+	+	+	4 ounces daily	4	
342342	12	W	F	12	1 mo.	+	+	+	+	+	+	+	+	4 ounces daily	5	12 days
341803	12	W	M	12	2 mo.	+	+	+	+	+	+	+	+	3 ounces daily	4	8 days
351931	13	W	M	?	?	+	+	+	0	0	+	+	+	3 ounces daily	6	8 days
341649	16	B	M	?	1 day ?	+	+	+	+	0	+	0	+	2 ounces daily	2	

an average value of 20 mg. of vitamin C per ounce of orange juice the amounts utilized varied from 80 mg. to 1,080 mg. with an average of 510 mg.

In view of the report of Ingalls,[17] who states that it requires about 2,000 mg. to saturate a scorbutic infant, it immediately becomes apparent that the curative dose for scurvy is far below the amount required to produce saturation of the body.

Since it requires an average total dose of 300 mg. to 500 mg. of ascorbic acid to produce clinical remission of scurvy over a variable period of days, it seems that a more rational procedure would be to give the scorbutic infant one large dose of crystalline vitamin C at the beginning of therapy, e.g., 500 mg. Then on the following three or four days this dose could be repeated daily until 2,000 mg. have been given, this latter figure being the dose which Ingalls states to be necessary to produce saturation. Following this, the infant can be placed on a maintenance dose of 25 to 50 mg. daily.

As stated before, there is a considerable lag in the time between the disappearance of the clinical manifestations of scurvy and the appearance of healing in the x-ray plates. The following typical case illustrates this point:

M. J., a 14-month-old colored female infant, was admitted to the Children's Hospital of Philadelphia on July 6, 1937, with frank evidence of scurvy. She lay in the pithed-frog position, cried when handled, and had intensely swollen hemorrhagic gums. Forty-eight hours after she had been given 500 mg. of ascorbic acid intravenously, she moved her limbs freely and did not object to handling, and the swelling of her gums had begun to subside. However, serial x-rays of the bones did not show any change indicative of healing until eleven days after this single dose. Thereafter, there was progressive healing in the bones as shown by the roentgenograms.

TEMPERATURE

Fever is known to be a common accompaniment of scurvy. A review of 56 cases of scurvy (Table III) seen on the hospital wards during the past five years and including the 21 cases treated with crystalline

TABLE III

TEMPERATURE IN SCORBUTIC INFANTS

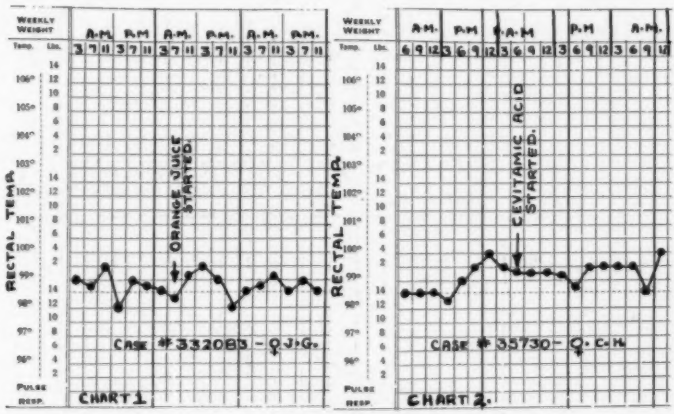
	NUMBER OF INFANTS
Afebrile infants with no infection, fracture, or large subperiosteal hematoma	9
Febrile infants with no infection, fracture, or large subperiosteal hematoma	7
Febrile infants with fracture or large subperiosteal hematoma	9
Febrile infants with infection	31
Total	56

vitamin C, reveals that 47 cases, or 84 per cent, were febrile at the time of admission. However, one must use caution in attributing the fever in these cases to the avitaminosis per se, for in 31 of the febrile cases infection was present, usually of sufficient severity to account

for the elevated temperature. Of the remaining 16 febrile uninfected patients, 9 had either large subperiosteal hematomas or severe fractures which could have accounted for the rise in temperature. Thus in a scorbutic infant who is not infected and who does not have a large subperiosteal hemorrhage or a fracture, fever is just as likely to be absent as present.

It has been said that following the institution of specific therapy in the scorbutic infant there is often a rise in temperature.[18, 19] This point was investigated in several of the afebrile patients in the following manner:

Rectal temperatures were taken at intervals of two or three hours for periods of twelve to twenty-four hours before vitamin C was administered and for twelve to twenty-four hours afterwards. In all cases but one there was no apparent temperature elevation. In this



Charts 1 and 2.—Temperature charts of two scorbutic infants showing that the temperature does not rise in the scorbutic infant after the administration of vitamin C.

one case the fever was found to be due to an incipient respiratory infection. Charts 1 and 2 represent the temperature curves in two such afebrile infants, one treated with orange juice and the other with ascorbic acid.

INFLUENCE OF VITAMIN C UPON THE BLOOD

Anemia is a common finding in the scorbutic infant. Parsons and Smallwood[20] have given an excellent review of this feature of this disease. While there are several complex factors such as infection, hemorrhage, and inadequate iron intake, which could be responsible for this anemia, Weill and Mouriquand[21] in 1922 demonstrated that vitamin C was necessary for hemoglobin formation. This has since been confirmed by other observers, most strikingly in a case of adult scurvy reported by Minot and Castle.[22]

The effect of ascorbic acid upon the anemia of scurvy was studied in five infants who were free from infection. Many other infants who were studied had to be omitted from consideration because they were transfused or were given iron therapy along with vitamin C. In each infant studied hemoglobin estimations (Sahli) and red cell and reticulocyte counts were done at intervals before and after the administration of vitamin C. Charts 3 to 7 depict the findings in the five infants.

Chart 3.

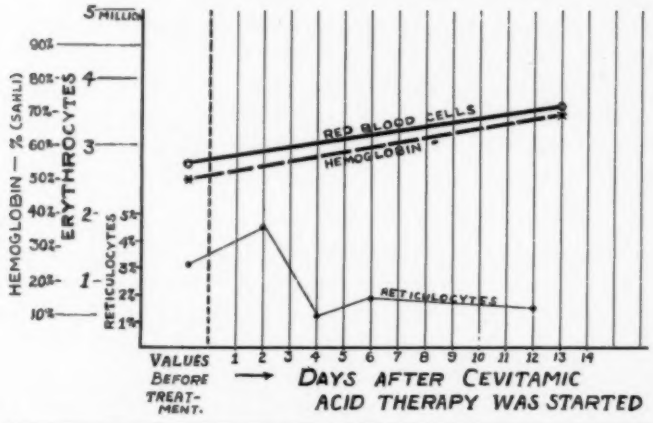
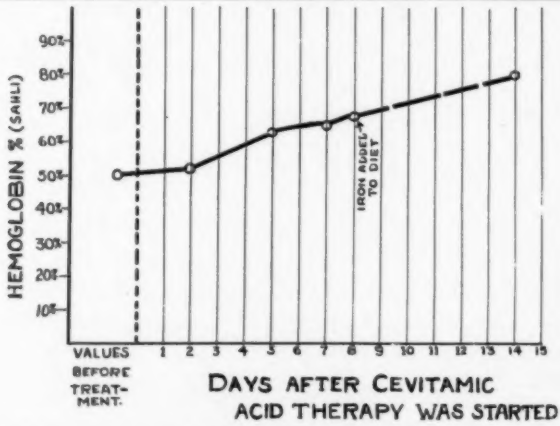


Chart 4.



Charts 3 and 4.—Case 1, M. L. H., female, and Case 2, W. C., male, respectively. Responses of hemoglobin, red blood count, and reticulocytes in the scorbutic infant following the administration of ascorbic acid.

In Case 1 (Chart 3) there was a significant increase in the hemoglobin and erythrocyte counts thirteen days after therapy was begun. It is difficult to state whether or not the 4.5 per cent reticulocyte value represents a response to therapy, inasmuch as there were 3 per cent reticulocytes prior to institution of therapy.

In Case 2 an increase of 18 per cent in hemoglobin, from 50 per cent to 68 per cent, took place eight days after the beginning of therapy (Chart 4). At this time iron was added to the diet.

The patient in Case 3 developed a steep reticulocyte rise from 1.2 per cent to 5.8 per cent one day after therapy (Chart 5). While there was no increase in the hemoglobin for 13 days, the red cells increased from 2.4 to 3.99 millions.

In Cases 4 and 5 no significant change was noted in the hemoglobin, red cells, or the reticulocyte values following the institution of therapy.

Parsons states that vitamin C is essential to normal hematopoiesis and that it is probably a factor essential to the maturation of the red cell. Minot reports that in a case of adult scurvy, in which iron was ineffective, a prompt hematopoiesis was induced by orange juice. Cases

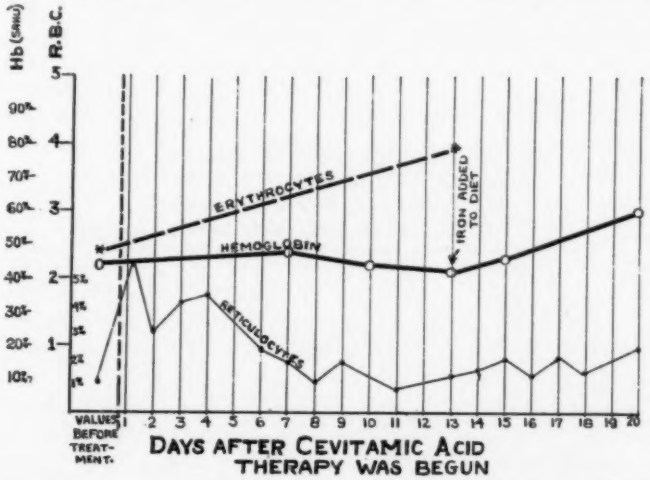


Chart 5.—Case 3, M. J., female. Responses of hemoglobin, red blood count, and reticulocytes in the scorbutic infant following the administration of ascorbic acid.

1, 2, and 3, above, might be cited as examples of the specific effect of vitamin C on the anemia of infancy. The effect of iron on the anemia of scurvy in the absence of vitamin C therapy was not studied in this group since it did not appear justifiable to withhold specific therapy in infants with acute symptoms of scurvy. However, it seems reasonable to assume from the results which Minot obtained that iron alone would be ineffective. At this point one wonders whether or not the failure of some anemic infants and children to respond to iron therapy might not be due to inadequate vitamin C intake.

In Cases 4 and 5 in which no response in hemoglobin or red cell formation was noted following the administration of vitamin C, it is possible that the iron reserve in these infants was so depleted that no iron was available for hemoglobin formation. This would seem to be a logi-

cal conclusion, for the diets of these scorbutic infants were inadequate in iron-containing foodstuffs, usually being limited to boiled milk. In those infants manifesting a response in hemoglobin formation after administration of vitamin C, one must assume that there was still some iron reserve even though these infants were also on inadequate diets.

Chart 6.

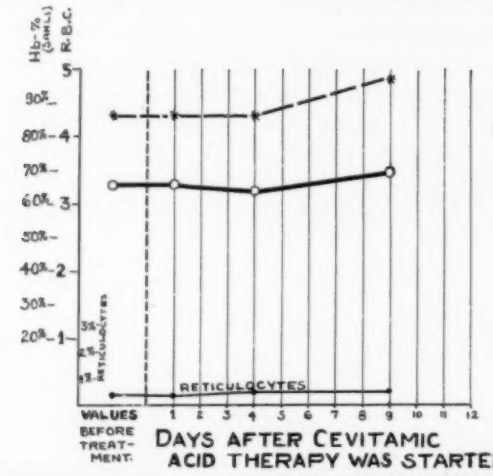
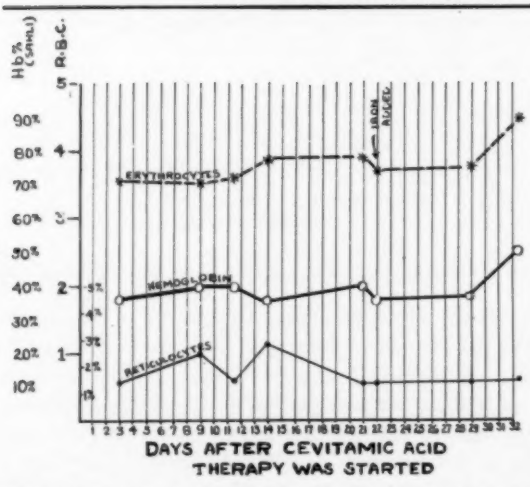


Chart 7.



Charts 6 and 7.—Case 4, S. A. H., female, and Case 5, L. C., male, respectively. Responses of hemoglobin, red blood count, and reticulocytes in the scorbutic infant following the administration of ascorbic acid.

Platelet counts and estimations of bleeding and clotting time as well as clot retraction were done on many of the infants. In almost all instances they were within normal limits. Therapy had no significant effect on any of these factors. In one case determinations of the serum proteins before therapy was begun gave values that were normal, viz.,

albumin, 4.8 gm. per cent; globulin, 2.1 gm. per cent; total, 6.9 gm. per cent. In two other cases in which the total serum proteins were determined three days after ascorbic acid therapy was begun, the values were normal, viz., 7.05 and 6.85 gm. per cent.

EFFECT OF VITAMIN C ON CAPILLARY RESISTANCE

Hemorrhage in scurvy has been attributed to increased capillary fragility. Wolbach and Howe[23] have stated that vitamin C is essential to the integrity of the capillary wall, in that it is necessary to the formation of the cement substance between its cells. Many attempts have been made to diagnose subclinical scurvy or latent scurvy, utilizing estimations of capillary fragility, i.e., from measurements of negative or occluding pressure which will produce petechiae when applied to an extremity. Göthlin[24] has applied this method extensively in such studies. However, Abt, Farmer, and Epstein[25] have not been able to obtain exact correlation between the vitamin C starvation and capillary resistance.

The influence of ascorbic acid upon capillary fragility was studied in 13 scorbutic infants. The following technique was used:

A blood pressure cuff was applied to the upper arm and inflated to about 50 mm. of mercury pressure. This pressure was maintained for about three to five minutes. The presence or absence of petechiae on the forearm was noted following this procedure. No attempt was made to count the number of petechiae, the tests being interpreted as positive or negative depending on the presence or absence of petechiae.

Petechiae were noted in 12 of the 13 infants before therapy was begun. Following the administration of ascorbic acid, the capillary resistance increased in 2 infants, as evidenced by negative tests on the fourth and seventh days after institution of therapy. In the remaining 10 infants in which the tests continued positive, it is possible that the period of observation was too short in duration. While petechiae can usually be produced in a scorbutic infant, it is our belief that the administration of vitamin C in amounts sufficient to initiate clinical healing of scurvy will not always produce early disappearance of this phenomenon.

In view of the many reports in which ascorbic acid had supposedly exerted beneficial effects upon hemorrhagic conditions, one patient with hemorrhagic nephritis in a subacute form was given ascorbic acid to determine whether or not any benefit might accrue. Summary of her case history follows:

C. B., an 11-year-old white girl, was admitted to hospital Nov. 29, 1937, complaining of frequent nosebleeds which had first appeared five days previously. She had no other complaints on admission other than those coincident to a mild upper respiratory infection. However, her state of nutrition was so poor that it was decided to admit her for investigation.

Physical examination showed a poor state of nutrition, pallor of skin, and mucous membranes. There was a deviation of the nasal septum, reddish boggy swelling of

the turbinates, and a moderate amount of mucoid nasal discharge. There was evidence of blood clot in the posterior nares. The examination was otherwise essentially normal.

Laboratory investigation on admission showed the urine to be yellow, acid, with a specific gravity of 1.012 and with a trace of albumin. There was an occasional red blood cell, as well as a similar number of white cells; red blood cells, 3.8 million; white blood cells, 9,500; hemoglobin, 9.8 gm.

Progress.—Two days after admission the patient began vomiting, following cauterization of the bleeding point on her nasal septum. At this time her blood pressure was 112/85 to 108/86. There appeared a soft systolic apical murmur which was transmitted a short distance toward the axilla. Blood urea nitrogen readings on this day and the day following were 56 and 70 mg. per 100 c.c., respectively. From this time on evidences of hemorrhagic nephritis became more apparent, with considerable excretion of red cells in the urine. The disease gradually subsided until a subacute stage was reached and on March 17, 1938, it was decided to give her 300 mg. of ascorbic acid daily by mouth. Addis counts were done on a number of occasions before and after the initiation of therapy. The following are the red cell estimations as determined by the twelve-hour Addis routine:

DATE		RED CELL COUNT
1/25/38		100,650,000
2/7/38		17,080,000
2/9/38		57,960,000
2/23/38		28,952,000
3/9/38		25,668,000
3/17/38	Ascorbic acid—300 mg. daily to 4/15/38	
3/22/38		7,420,000
3/25/38		18,104,000
3/29/38		32,976,000
4/2/38		16,732,000
4/12/38		34,776,000
4/15/38		53,550,000

Obviously the hematuria has not been cured by this form of therapy.

EFFECT OF ASCORBIC ACID ON WOUND HEALING

That vitamin C depletion interferes with wound healing was pointed out in 1924 by Saitta.[26] Wolbach and Howe[27] studied the healing process in scorbutic guinea pigs more extensively and came to the same conclusion. Ingalls and Warren[28] have made more extensive experimental and clinical observations on the influence of latent scurvy on poor wound healing and present fairly conclusive evidence concerning the relationship between these two conditions. It would seem to be a reasonable procedure to saturate an infant with vitamin C prior to operation in order that wound healing might be insured.

The following is a case report of an infant, operated upon for pyloric stenosis, in whom wound healing was apparently stimulated by the administration of ascorbic acid:

J. C., a 27-day-old first-born white male, was admitted to hospital with a history of persistent vomiting beginning on the fourteenth day of life. The infant had been born in hospital after a normal gestation and labor; birth weight 6 pounds, 8 ounces. During the first two weeks of life the child had been offered breast milk every four hours and had gained to 8 pounds, 6 ounces at the time of leaving the hospital. Progress was quite satisfactory until about the fourteenth day of life

when he began to vomit, only occasionally at first, but before long after every feeding. No stool had been passed for two days prior to admission, and a diaper rash had been present for ten days.

Physical examination revealed a dehydrated and undernourished infant weighing 6 pounds, 5 ounces. Visible peristalsis was present, and a mass was palpable in the right upper abdomen. A diagnosis of pyloric stenosis was made.

Laboratory findings on admission showed red blood cells, 4.03 million; white blood cells, 9,900; hemoglobin, 13 gm.; CO_2 combining power, 56 vol. per cent; chlorides, 560 mg./100 c.c.; Wassermann reaction, negative.

Following several blood transfusions and the administration of saline and glucose intravenously, the infant was operated upon on the fifth day of hospitalization. A Fredet-Rammstedt procedure was carried out with the aid of local anesthesia. Following the operation, the incision showed no evidence of healing and became boggy and edematous on the fourth post-operative day, while the following day the wound broke down with the evisceration of a segment of transverse colon. On the same day repair was carried out. However, for two days following the repair, the wound showed no evidence of healing. At this time 300 mg. of ascorbic acid were given intravenously. On the following day evidence of healing was noted for the first time. Subsequent healing was progressive, and the remainder of the hospital stay uneventful.

THE EFFECT OF SCURVY ON THE HEART

In six infants teleoroentgenograms revealed an increase in the size of the heart. It is difficult to state whether or not this cardiac enlargement is due to the scurvy per se, for, as has been pointed out, the scorbutic infant may be suffering from multiple latent dietary deficiencies. Thus the cardiac enlargement could well be due to vitamin B_1 deficiency or in part due to anemia. That these factors rather than vitamin C deficiency may be operative in producing a cardiac enlargement would seem borne out in one case in which roentgenograms taken at intervals after the scurvy had been cured showed no decrease in the size of the heart. In all six infants there was a marked degree of anemia, the initial hemoglobin values ranging from 30 per cent to 55 per cent (Sahli), the individual values being 30, 36, 44, 50, 54, 55 per cent (average 45 per cent).

We are appending complete case histories of three infants with infantile scurvy who were treated with crystalline vitamin C that we may bring out more fully the clinical course of the scorbutic infant treated in this manner.

CASE 1.—M. J., a 14-month-old colored female, one of full-term twins, was admitted to the Children's Hospital of Philadelphia on July 6, 1937, with a diagnosis of scurvy.

The past history was negative apart from the features relative to the scurvy; the developmental history was unreliable. Feedings had consisted of breast milk for two weeks, dryco formula for four weeks, followed by an evaporated milk, water, and karo mixture, which had been given up to the time of admission to hospital.

Cod-liver oil had been given in ½ teaspoon amounts daily from the age of 10 months, but no orange juice or other antiscorbutic had ever been offered.

The illness leading to admission began insidiously about the age of 9 months, at which time the infant's gums became swollen and hemorrhagic. At about this same time the right thigh became swollen, and, on consulting the local doctor in a rural Virginia community, the mother was informed that the baby had rheumatism.

However, no alteration was made in the diet. Following this, the infant lost weight, the gums bled intermittently, and increasing pallor developed. In addition, sweating, thirst, and salivation became very evident. Both legs became swollen, and the infant was loath to move them about. During the week prior to admission she became fretful and refused practically all of her food with the exception of small amounts of milk.

Physical examination showed the baby to be underdeveloped and undernourished as well as acutely ill. Her weight was 12 pounds, 2 ounces. She was irritable and cried when touched. The anterior fontanel measured 2 by 2 cm. There was marked pallor of the skin, mucous membranes, and lips. The tongue was coated. Two upper and three lower central incisors were present; the gums were greatly swollen, purplish, boggy, and oozing blood. The costochondral junctions were hard, sharp, and angulated. On percussion the heart appeared to be enlarged to the left. Over the upper half of the right femur was a palpable mass. All the joints were movable, but movement was resisted.

X-ray examination on admission showed rings about the epiphyseal centers with ground-glass appearance of the areas within. There was thinning of the cortex and increased density of the zones of temporary calcification. There was also distinct cupping of the ends of the diaphyses with osteoid zones typical of rickets. There was a varus deformity of the upper femoral epiphysis. The 6-foot film of the chest showed slight enlargement of the heart to the left. The rib ends showed a marked rosary.

Laboratory findings on July 6 showed fragility, 0.22-0.44; clot retraction, normal; blooding time, 1 minute; coagulation time, 4 minutes 39 seconds. On July 12 the blood calcium was 10.9 mg. per 100 c.c. and the serum phosphorus was 4.5 mg. per 100 c.c.

	R.B.C. (MILLIONS)	W.B.C.	HEMOGLOBIN	RETICULOCYTES
7.6	2.4	9,500	44%	1.2%
7.7				5.8
7.8				3.0
7.9				4.0
7.10				4.4
7.12				2.4
7.13			48%	1.9
7.14				1.1
7.15				1.1
7.16			44%	
7.17				0.9
7.19	3.99		41%	1.4
7.20				1.6
7.21			46%	2.0
7.22				1.4
7.23				2.1
7.24				1.5
7.26			60%	2.4
8.2	4.18 (8/13/37)		68% (8/2/1937)	

Treatment.—On July 6, 1937, 500 mg. of ascorbic acid dissolved in 50 c.c. of hypotonic saline (half isotonic) were given intravenously. On July 9 the administration of a dram of 20 per cent iron and ammonium daily was begun. The patient was placed on a Bradford frame with Buck's extension for treatment of the coxa vara.

Progress.—The bleeding and swelling of the gums had entirely disappeared six days after the single intravenous dose of ascorbic acid. The varus deformity responded to treatment, and the patient was removed from the frame after about five weeks. X-ray pictures taken four days after the beginning of therapy showed no

evidence of healing while a repetition of the series on the eleventh day showed slight progress of the healing process. On the twentieth day there was increased calcification at the distal end of the femur around the lateral spurs with additional increase in the density of the zones of temporary calcification. At this time 50 mg. of ascorbic acid were added to the daily diet. During the fifth week the coxa vara deformity showed less angulation, especially on the right side.

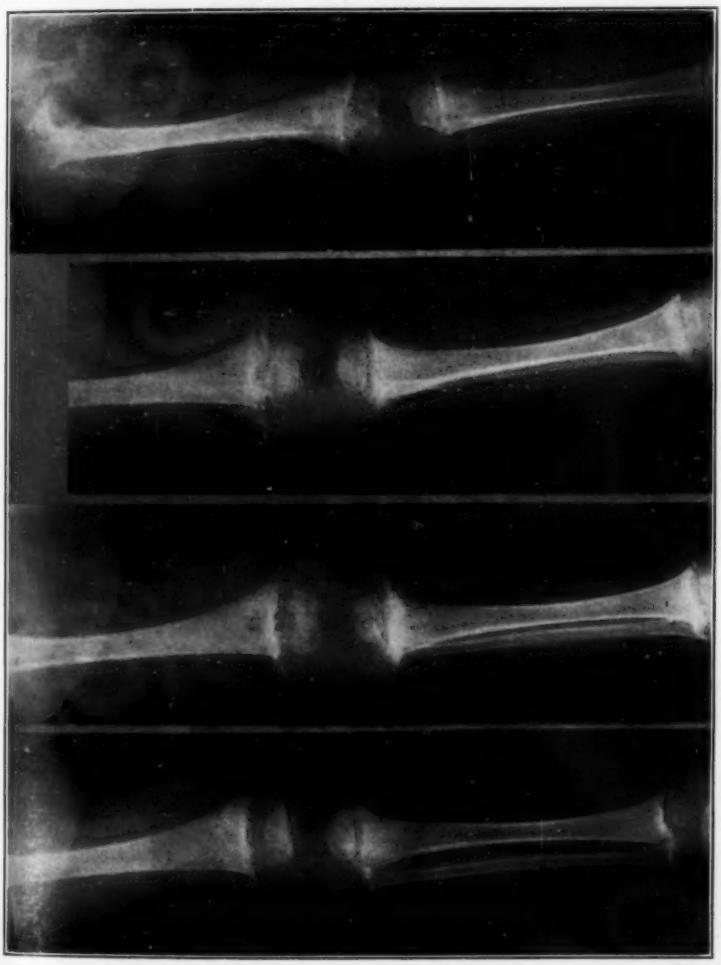


Fig. 1. Fig. 2. Fig. 3. Fig. 4.

Figs. 1 to 4.—Case 1. M. J. *1*, X-ray plate taken on admission showing marked evidences of scurvy. *2*, X-ray film taken nineteen days after initiation of ascorbic acid therapy, showing beginning healing. *3*, X-ray plate taken twenty days after beginning of therapy, showing advance of healing. *4*, X-ray plate taken nine weeks after beginning of therapy, showing complete healing.

Six weeks after admission the contour of the heart shadow was still abnormal, the transverse diameter being 8 cm. in comparison with a thoracic breadth of 12.5 cm.

Figs. 1 to 4 are roentgenograms of this patient, illustrating the progressive healing of the scorbutic process.

Case 2.—S. C., a 10-month-old white female infant, was admitted to hospital on Feb. 25, 1935, with a diagnosis of lobar pneumonia and scurvy with retrobulbar hemorrhage.

The infant was the result of a full-term pregnancy and normal delivery. Birth weight was 6 pounds 14 ounces. She was breast fed for one month and thereafter given fresh milk, water, and karo. She received no solid food since she had always refused it. Cod-liver oil was given in uncertain amounts until one month prior to admission. No orange juice or other antiscorbutic had ever been offered.

At the age of 7 months the infant was hospitalized at another Philadelphia hospital because of bronchitis and otitis media. After discharge a cough of insignificant nature persisted. One week prior to admission to the Children's Hospital of Philadelphia the cough became worse, and a nasal discharge developed. Four days later shortness of breath supervened, and the cough became "dry and difficult." Apart from the manifestations of scurvy, the past and family histories were inconsequential.

One month prior to admission the monther noticed that the child began to cry on being picked up. She refused to sit and objected when her legs were handled. The family physician was consulted and a diagnosis of "muscle soreness" made. At about this time it was noticed that the infant had "bumps on her ribs." As these enlarged, the front of the chest "sank in." Two weeks prior to this time a hemorrhage developed in the upper lid of the left eye which gradually cleared up only to reappear the day before hospital admission. About one week before admission the left eye became prominent. Three days prior to admission the upper parts of both thighs were found to be enlarged and firm. The day before admission the feet became swollen.

Physical examination showed the infant to be extremely pale, lying in the pithed-frog position. She was dyspneic, irritable, and obviously quite ill. The skin was pale and waxy; there were numerous small petechiae over the chest and in the upper left lid as well as the right lower lid. The anterior fontanel was patent. The left eye protruded about ¼ inch beyond the right but the movements were not impaired. The left tympanic membrane was mildly congested; a moderate amount of mucopurulent discharge was present in the anterior nares. No teeth had erupted. The costochondral junctions were markedly beaded, and the sternum was depressed. There were signs of pneumonia over the right lower lobe. The upper parts of both thighs were enlarged, the masses being deep, firm, and moderately swollen.

On admission x-ray films of the long bones showed typical changes of scurvy in the prehemorrhagic stage, except at the upper ends of the diaphyses of the femurs where vague signs of hemorrhage were present. In the chest film the ribs showed a marked rosary which was thought to be of scorbutic origin because of the increased density of the zones of temporary calcification at the rib ends and the framework marrow zones just behind them.

Laboratory findings were as follows: Urine was negative.

DATES	R.B.C. (MILLIONS)	W.B.C.	HG
2/25/35	2.45	15,000	35%
2/27/35	2.85	13,500	46
3/ 1/35	2.30	11,900	58
3/ 2/35	4.00	15,100	52
3/ 3/35			65
3/ 5/35	4.20	9,000	69
3/ 8/35			72
3/13/35			78
3/22/35			78

On Feb. 27, 1935, the reticulocytes numbered 3 per cent; bleeding time was 1 minute 30 seconds; platelets, 240,000; venous coagulation time, 3 minutes 45 seconds. Clot retraction was marked; fragility, 0.46 0.22; tourniquet test, positive; albumin, 4.7 gm.; globulin, 1.3 gm.

On March 21 the reticulocytes were 0.9 per cent.

Treatment.—On February 25 100 mg. of ascorbic acid were given intravenously along with a small amount of equal parts of distilled water and normal saline. A 50 mg. dose was continued daily by mouth from February 25 to April 4. In addition repeated transfusions were given, beginning the day following admission.

Progress.—The presence of the pneumonic process made the clinical evaluation of the response to antiscorbutic therapy difficult, but six days after the institution of treatment the general condition was greatly improved. A pneumonic crisis devel-

Fig. 5. Fig. 6.

Figs. 5 and 6.—Case 2. S. C.

Fig. 5 is the x-ray plate taken on admission, showing evidences of scurvy.

Fig. 6 is the x-ray plate taken eighteen days after beginning of ascorbic acid administration, showing marked healing.

oped on the tenth hospital day, following which the pneumonia cleared without complications. Eight days after admission the left shoulder became swollen, tense, and hot. X-ray examination confirmed the diagnosis of epiphyseal separation. An extension splint was applied and kept in place for about three weeks.

The presence of pneumonia in this child undoubtedly must have retarded the healing of the scorbutic process as calcification did not appear in the x-ray film

until the eighteenth day of treatment and both legs remained swollen for thirteen days. Healing was not evident in the x-ray plate on the seventh day, but on the eighteenth day there was evidence of beginning repair.

Figs. 5 and 6 are roentgenograms of this patient, taken on admission and eighteen days later, respectively.

CASE 3.—M. L. H., an 8-month-old colored female infant, was admitted to the Children's Hospital on June 30, 1936, with a diagnosis of scurvy with retro-orbital hemorrhage.

The infant was born at home after a full-term pregnancy and normal delivery. The birth weight was 7 pounds. The past history was inconsequential except for the presence of a brief upper respiratory infection at the age of 5 months. Breast milk had never been given, but instead a similac formula. This was fed in increasing amounts until two weeks prior to admission, when cow's milk was substituted. Cod-liver oil was begun at the age of 3 months and continued in daily doses of 1 teaspoonful. Tomato and orange juice, though offered, had always been refused. Vegetables, mainly mashed potatoes, were added at the age of 8 months.

The illness leading to admission began about two months earlier when the mother noticed both legs to be swollen and tender. The arms also were tender although not obviously swollen. The family physician was consulted, and a diagnosis of "muscular rheumatism" made. Only on being moved did the infant show any signs of irritability. Three days before admission to the hospital the left eye became swollen and prominent, and remained so until the time of admission.

Physical examination showed the patient to be a moderately well-developed and poorly nourished, pale colored infant. A diaper rash was present over the buttocks, and a few pyogenic skin lesions scattered over the face and chest. Both eyes were prominent, but the left was definitely exophthalmic with considerable swelling of both upper and lower lids. The sclerae and conjunctivae were muddy. Two lower central incisors had erupted, and the adjacent gums were red, spongy, and easily made to bleed. The costochondral junctions were sharply beaded. Percussion of the left heart border gave rise to the suspicion that it extended out slightly beyond the midclavicular line. All four extremities appeared swollen, tense, and otherwise abnormal in that the distal ends of the radii, ulnae, and tibiae were all enlarged.

X-ray examination on admission showed dense zones of temporary calcification with typical framework marrow zones about the epiphyseal centers, characteristic of scurvy in the early healing stage. There were lateral spurs and evidence of small

DATES	R.B.C. (MILLIONS)	W.B.C.	HG	RETICULOCYTES
June 30				3.1
July 1	2.66	9,850	53%	
July 3				4.5
July 6				1.9
July 7	3.22		55	
July 13	3.58		69	1.9
July 15				1.2
July 17				1.6
July 18	3.55		62	1.8
July 23				1.3
July 24	3.50		59	

subperiosteal hemorrhages. There was also mild cupping. The chest showed a definite rosary but no evidence of cardiac or pulmonary pathology.

Laboratory investigation on admission showed urine, negative; Wassermann reaction, negative; fragility, 0.42 to 0.24; bleeding time, 2 minutes 9 seconds; platelets, 435,000; and venous coagulation, 3 minutes 12 seconds.

Treatment.—The patient was given 50 mg. of ascorbic acid daily by mouth for five days and thereafter 20 mg. daily by mouth.

Progress.—Regression of the signs began within forty-eight hours, and thereafter was progressive. Within ten days the arms and legs were no longer tender when moved, and by the end of the twenty-first day the eye was normal in appearance. X-ray signs of healing, however, first became apparent about the seventeenth day after the institution of therapy.

Fig. 7. Fig. 8. Fig. 9.

Figs. 7, 8, and 9.—Case 3. M. L. H.

Fig. 7 is an x-ray picture taken on admission showing evidences of scurvy.

Fig. 8 is a roentgenogram taken nine days after institution of ascorbic acid therapy, showing practically no healing.

Fig. 9 is a roentgenogram taken seventeen days after beginning of ascorbic acid therapy, showing good healing of the scorbutic process.

SUMMARY

1. Nineteen infants were given crystalline vitamin C* in the dosage of 1.83 mg. per kg. daily for a period of five months as a prophylactic against scurvy. No clinical or roentgenologic evidence of scurvy was apparent during the period of observation.

2. Crystalline vitamin C was used in the treatment of 21 cases of infantile scurvy. Satisfactory healing was obtained in all instances. A

brief analysis of the amounts of the vitamin necessary to produce clinical healing is presented.

3. The presence and significance of fever in the scorbutic infant are analyzed, and the lack of temperature elevation following the administration of vitamin C is pointed out.

4. A study was made of the hematopoietic response following the administration of crystalline vitamin C.

5. There was no constant effect produced upon the capillary resistance (capillary fragility test) in our scorbutic infants following the administration of vitamin C.

6. A brief discussion of the effect of scurvy upon the heart is given.

7. Crystalline vitamin C seemed to stimulate wound healing in the incision of an infant operated upon for pyloric stenosis in whom there was no evidence of healing prior to its administration.

8. Intravenous administration of vitamin C seemed to have no effect on the hematuria in a case of subacute hemorrhagic nephritis.

9. Complete case histories of three scorbutic infants treated with crystalline vitamin C are given.

We wish to express our thanks to Merck & Co., Inc., for their generosity in supplying the ascorbic acid used in these studies.

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EPIDEMIC DIARRHEA OF THE NEWBORN

A Report of Three Outbreaks

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IN THE last two years attention has been focused on outbreaks of "epidemic diarrhea of the newborn" of unknown etiology which have appeared in a number of cities. The epidemiology, bacteriology, pathology, and clinical features of this condition have been carefully reviewed by Rice, Frant, and their co-workers[1] within the past year.

The purpose of this paper is to report three epidemics of diarrhea in the newborn period which occurred in the New York Hospital from 1935 to 1938. In this institution the nurseries for full-term newborn babies are in the obstetrical building, but the medical care of the babies is under the direct supervision of the pediatric staff. Prematurely born infants are transferred to a special suite in the pediatric building which consists of two air-conditioned nurseries of seven beds, each with individual utility room, and an unconditioned nursery of six beds. This arrangement permits the segregation of "infected" from "clean" infants, whenever necessary.

FIRST EPIDEMIC

The first outbreak occurred in one of the obstetrical nurseries in October, 1935. It began insidiously with the appearance of semisolid stools in two babies. The following day another infant was similarly affected. On the third day nineteen more babies were stricken, and it was then realized that a diarrheal condition of epidemic proportions had developed.

The affected babies were taken off breast feedings and isolated on an unused pediatric pavilion of twenty-eight beds with the nursing staff of the single obstetrical nursery affected in attendance. Admissions to the obstetric pavilion adjacent to the affected nursery were stopped, and finally the entire unit, including rooms for the mothers, nursery, utility rooms, and halls, was washed and painted. New cases continued to appear in this nursery for the following two or three days and then stopped abruptly.

Fifty-nine in a total census of 337 exposed infants were affected, a morbidity rate of 17.5 per cent. Their age at onset varied from two to fourteen days. The condition was apparently unrelated to the type of feeding, for seventeen of the stricken babies had been breast fed, seven

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formula fed, and thirty-five had received mixed feedings. The stools were loose, yellowish-green, occasionally contained mucus, but never blood or pus. Vomiting was rare. All the infants continued to gain weight except one, who became dehydrated and acidotic, necessitating starvation and the administration of parenteral fluids.

In an effort to isolate the exciting agent and to determine the mode of transmission, careful bacteriologic studies were made of possible vectors including nipples, baby oil, ammoniated mercury ointment, linen, formula room attendants, nurses, and nursery attendants. These studies failed to reveal any organisms of presumably epidemiologic significance. In addition, nose and throat cultures and repeated bacteriologic examination of the feces of all the affected infants were made with similarly inconclusive results. The organisms cultured from the stools were varied and included *B. coli mutabile*, hemolytic *Staphylococcus aureus, Staphylococcus albus, B. subtilis, B. coli, Alpha streptococcus, Gamma streptococcus* and *B. lactis aerogenes*. The variability of these organisms, the marked fluctuation in number of colonies isolated, and the fact that they may be found in the fecal flora of normal infants indicated that no etiological role could be ascribed to any of the isolated organisms.

Despite the extent of the epidemic, it was apparently of mild character since all of the infants recovered, usually within a period of two or three days with a maximum of one week. The therapy consisted of isolating the infants and the administration of whole lactic acid milk without added sugar, in amounts adequate to cover the fluid requirement of each child. There were no fatalities although some patients remained as long as a week after the mother's discharge. All patients were discharged from the hospital in good condition, 40.7 per cent being above birth weight.

While a complete follow-up of these cases was not made, no evidence was found to indicate that these infants were subsequently more susceptible to true gastrointestinal intoxication.

SECOND EPIDEMIC

The second outbreak of diarrhea occurred in the air-conditioned premature nursery in October, 1937, two years after the first outbreak. Two previously normal, thriving premature infants developed frequent, loose, blood-tinged, mucoid stools, and in the following two months a total of thirteen premature infants were likewise affected. During this time the daily census ranged from four to twelve babies; in all, sixteen infants were exposed, giving a morbidity rate of 81 per cent.

The weights of the infants at the time of onset of diarrhea ranged from 1,350 grams to 2,260 grams. Their ages ranged from four to nineteen days with the exception of one infant who was seventy-five days old when afflicted. The duration of illness (with the exception of one death at four days) varied from nine to fifty-nine days and averaged eighteen

days. The number of stools ranged from seven to eleven and averaged nine per day throughout the course of the illness. Vomiting was not a prominent feature.

The diarrhea was apparently unrelated to the type of feeding; six children had been fed human milk, four human milk plus calcium paracaseinate, and three an evaporated milk formula containing dextrimaltose.

In this epidemic extensive bacteriologic studies of patients' stools, nipples, formulas, and nose and throat cultures of the nursery personnel failed to reveal the source of the outbreak. In contradistinction to the previous epidemic, however, cultures of the stools in nine of thirteen patients with diarrhea and in one without symptoms* revealed organisms (*B. coli mutabile* or hemolytic *B. coli*), which some workers have regarded as pathogenic.

The significance of these bacteriologic findings cannot be evaluated with certainty. In 1935 Dulaney and his co-workers[2] found *B. coli mutabile* in the stools of 67 per cent of the patients in an epidemic of diarrhea of the newborn.

TABLE I

STOOL CULTURES OF ALL PREMATURE INFANTS EXPOSED IN EPIDEMIC OF DIARRHEA, OCTOBER, 1937

ORGANISM	PATIENTS WITH DIARRHEA (13)		PATIENTS WITHOUT DIARRHEA (3)
B. coli multabile	1		1
Hemolytic *B. coli*	1		
B. coli mutabile Hemolytic *B. coli*	3		
B. coli mutabile Hemolytic *B. coli* Nonhemolytic streptococci	3	9	
B. coli mutabile Nonhemolytic streptococci	1		
Nonhemolytic streptococci	4		
B. coli communis			2

Despite the presence of profuse diarrhea and bloody stools, all except two of the infants took their formulas well and continued to gain weight slowly. Two infants who refused feedings became dehydrated and acidotic, requiring cessation of oral feedings and the administration of parenteral fluids. Both succumbed in spite of this therapy.

The first infant, a colored female, weighing 1,300 grams at birth, was not thriving even before the onset of diarrhea at the age of seventy-five days. The second infant, a white male twin, weighing 1,380 grams at birth, had had atelectasis and attacks of cyanosis before the onset of the fulminating diarrhea which began on the third day of life and caused the infant's death on the fourth day of life.

*The twin of this subject had diarrhea as did two other sets of twins from whose stools the organism was grown.

In this epidemic there were two deaths in thirteen cases, a mortality rate of 15.4 per cent.

The infants with diarrhea were segregated in one of the two air-conditioned nurseries, and the other one was washed and painted in preparation for future admissions. Following discharge of all of the affected infants, the second room was similarly treated. Since that time there has been no diarrhea in the premature nurseries.

Follow-up study of the eleven infants who survived the diarrhea and of the three without diarrhea, all of whom were discharged from the hospital weighing well over 2,500 grams, revealed that twelve continued to thrive for at least six months after discharge and that the remaining two were readmitted to the hospital eighteen and thirty days, respectively, after discharge, suffering from acute gastrointestinal intoxication. In neither infant was *B. coli mutabile* or hemolytic *B. coli* isolated from the stools during the second admission.

THIRD EPIDEMIC

In the last week of January, 1938, approximately three months after the outbreak in the premature nursery, the third epidemic occurred, this time affecting four of the five newborn nurseries both private and pavilion. Only one pavilion nursery escaped. The first case made its appearance on January 21, and the last case on February 4. A total of thirteen cases developed in 212 infants who were exposed at this time, or a case morbidity rate of 6.1 per cent.

The onset in all thirteen infants occurred between the fourth and the thirteenth day of life and was insidious in character. A previously well baby developed many large, loose, watery, greenish yellow stools (seven to nine daily) without blood, pus, or mucus, and rapidly became dehydrated, showing the classical signs of cholera infantum. All finally exhibited a low alkaline reserve content of the blood. In this outbreak vomiting was quite frequent. At the time of onset, two infants had been fed exclusively at breast, seven were fed a cow's milk formula, and four were receiving a mixture of breast and cow's milk.

Epidemiologic studies again failed to reveal the source of the epidemic or the etiological agent. Repeated stool cultures from the affected cases showed no organisms which might be considered pathogenic with the exception of one infant whose stool showed an unidentifiable member of the salmonella group.[3, 4] Dysentery agglutinations of the blood[5] were negative in all instances.

As in the first epidemic, the affected cases were transferred to the pediatric service and admissions to the obstetrical service stopped until all the pavilions and nurseries had been washed and painted.

Four of the thirteen patients suffered from complications: (1) oral thrush; (2) sterile abscess of the right hip, cause undetermined; (3)

icterus gravis neonatorum; (4) paronychia of the right index finger followed by cellulitis and osteomyelitis of the two distal phalanges.

Although the number of patients affected in this epidemic was relatively small, it differed from the preceding ones, for all of the infants were extremely ill and required vigorous therapy. Accordingly, the regimen routinely used for treating gastrointestinal intoxication in older infants was instituted. With this therapeutic regimen the patient was completely starved, receiving not even water by mouth, until no stools had been passed for at least twelve and preferably twenty-four hours, and the carbon dioxide content of the blood had returned to its normal level. At the onset of this regimen, the infants received a hypodermoclysis of normal saline followed by an intravenous infusion of 10 per cent glucose in distilled water in order to initiate and maintain secretion of urine.

The fluid needs of the infant, calculated on the basis of approximately 150 c.c. of fluid per kilogram of body weight in twenty-four hours, were covered by parenteral administration of three intravenous infusions of 6 per cent glucose in distilled water and one hypodermoclysis of normal saline evenly spaced through each twenty-four hours. (The initial hypodermoclysis and hypertonic infusion were not included in this calculation.) If the blood carbon dioxide content was very low, the initial infusion usually consisted of a one-sixth molar lactate solution.[6] This solution was also used for the initial hypodermoclysis on occasion.

Beside these treatments, the patients received transfusions of 20 c.c. of citrated whole blood per kilogram on the first and second day of the regimen and as frequently thereafter as indicated.

Following the period of starvation, oral administration of fluid was begun. Sterile distilled water was offered every two hours beginning with amounts of 5 c.c. and increasing by 5 c.c. at alternate feedings until the patient was receiving his total fluid requirement by mouth. In the interim occasional parenteral treatments were given to cover the fluid needs. At this point, protein milk was substituted for water in 5 c.c. amounts and increased by 5 c.c. amounts at alternate feedings until the total fluid requirement was given as protein milk.

Then, on successive days, the frequency of feedings was decreased to ten, eight, and finally six feedings per day. The caloric intake was slowly raised during this time (preferably by not more than ten calories per kilogram per day) by the addition of calcium paracaseinate (7 per cent) or banana powder (5 per cent).

In those infants in whom there was no recurrence of loose stools, the formula was then gradually changed to one suitable for use following discharge from the hospital. From the time water was begun until an adequate formula was reached, seven to nine days elapsed. The feedings were never increased more rapidly than outlined above, regardless of how well the patient had responded.

As previously mentioned, this form of drastic therapy was used in all of the thirteen affected infants. The interval of complete starvation extended from 78 to 120 hours. Because of recurrence of loose stools in two of the patients, the therapeutic regimen was repeated on two and three occasions, the patient with icterus gravis being starved intermittently for a total of ten days.

The efficacy of this prolonged, exacting, and laborious form of therapy was demonstrated by the survival and complete recovery of all of the thirteen patients, despite the severe nature of the epidemic. Follow-up examination (only a four-month period at the time of writing) reveals that all these infants are progressing satisfactorily.

A comparison of some of the chief characteristics of these three outbreaks is shown in Table II.

TABLE II

COMPARISON OF EPIDEMICS

	(1) OCTOBER, 1935 OBSTETRICAL NURSERIES	(2) OCTOBER, 1937 PREMATURE NURSERY	(3) JANUARY, 1938 OBSTETRICAL NURSERIES
Number of affected cases	59	13	13
Morbidity case rate, per cent	17.5	81	6.1
Number of deaths	None	2	None
Mortality rate, per cent	0	15.4	0
Suspected organisms found on stool culture	Various organisms grown but not consistently enough to be significant	*B. coli mutabile* Hemolytic *B. coli*	None
Age at onset of diarrhea, days	2-14	4-19*	3-13
Duration of diarrhea, days	2-7	9-59	4-10
Clinical appearance	Good general condition. Good appetite (one exception)	Good general condition. Good appetite (two exceptions)	Dehydrated and toxic. Poor appetite
Treatment	whole lactic acid Isolation and milk	Isolation and no change in feedings	"Gastrointestinal regimen." 1. Complete starvation 78 to 120 hours followed by small amounts of water for 24-48 hours 2. Substitution of small feedings of protein milk for water 3. Parenteral fluids (saline, 6 per cent glucose in distilled water, transfusions)

*One exception was a premature infant seventy-five days old.

SUMMARY

Three outbreaks of epidemic diarrhea of the newborn, involving a total of eighty-five infants, were observed in the past three years.

1. Fifty-nine full-term infants were involved in the first, thirteen premature infants in the second, and thirteen full-term infants in the last outbreak.

2. The morbidity rates for the three epidemics were 17.5 per cent, 81 per cent, and 6 per cent, respectively.

3. The infants in the first and second groups were for the most part not sick clinically and responded to simple isolation with no drastic limitations in their feedings. The third group were all very sick and showed classic signs and symptoms of grave gastrointestinal intoxication. Vigorous treatment, including starvation, parenteral fluids, transfusions, and a careful slow resumption of feeding, resulted in no deaths in this group.

4. No definite pathogenic organism was found in the stools of the full-term infants. From the stools of 70 per cent of the premature infants *B. coli mutabile* or hemolytic *B. coli* or both were cultured.

5. The low morbidity rates in the full-term infants (17.5 per cent and 6.1 per cent) indicate the desirability of prompt drastic isolation measures.

6. The fact that there were no deaths in the third group of very sick infants indicates that in the neonatal period treatment as drastic as that used for older infants with gastrointestinal intoxication may, under certain conditions, be desirable.

CONCLUSIONS

In three epidemics of diarrhea in the newborn, the differences in the clinical syndromes, morbidity and mortality rates, bacteriologic findings, and therapy demonstrate the variable nature of this disease.

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525 EAST 68TH STREET

FACTORS INFLUENCING THE RELATION OF CONVULSIONS AND HYPERTHERMIA

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APPARENTLY normal, healthy children have been observed to experience one or more convulsions at the onset of an acute infection, the convulsion often being the first indication of disease. When the temperature is taken, it is usually found to be high. Although it may remain high, or swing in septic fashion, there are generally no more convulsions, and, after the disease has run its course, there are no neurologic residua. The etiology of the seizures is obscure. Many have considered the fever itself as the cause; others have implicated a toxemia from the infection. The latter explanation is open to the objection that the diseases associated with convulsions at their onset are many and varied and the toxemia continues after the convulsions have ceased. To consider hyperpyrexia alone as the cause brings up the question of the occurrence of the convulsions only at the beginning of the fever, without recurrence although the fever remains high. The explanation is then offered that the convulsions occur only when the fever rises suddenly and that it is the rapid change in temperature which is responsible. At the suggestion of Dr. Grover F. Powers this thesis has been submitted to experimental study, the results of which are reported in this communication.

LITERATURE

Review of the clinical literature dealing with the phenomenon under discussion is not very helpful. It has been pointed out that some patients who have this type of convulsion may develop epilepsy later while others remain normal.[1] Although Faerber[1] and Hochsinger[4] believed that the character of the infection must play a role, since convulsions are more common with certain infectious diseases than others, they failed to consider the possibility of the differences being due to variations in the type of fever curve associated with the several diseases.

The theory that fever alone can cause convulsions is supported by the fact that in human beings convulsions incidental to treatment of diseased patients have been reported after the use of diathermy[2]; radiant heat cabinet[13]; air-conditioned cabinet.[3] The temperature level reached and the speed of rise varied in each set of experiments. Most of the convulsions occurred during or immediately after the temperature rise, but in one instance[3] the convulsions were observed on the tenth day sub-

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sequent to the last of three treatments. "Clinical signs of tetany and occasional convulsions" were noted during the use of hot baths as a means of raising the temperature of supposedly healthy young adults.[5]

The association of fever and convulsions in animals was observed by Welch[14] in 1888. When the temperature of rabbits was raised rapidly to 111-113° F., the animals had convulsions, and death followed. When the heating was increased slowly, the animals could be kept at 107° F., for as long as three weeks without ill effects. Convulsions have been also observed in rats[12] after temperature elevations of about 5° C. produced by high frequency current. Irritability during the rise, but not during the maintenance of fever, was noted in dogs treated by a similar apparatus.[8]

The pathological changes found in the brains of sick human beings who have died after treatment in an air-conditioned cabinet include perivascular hemorrhages, destruction of Nissl substance, and shrinkage and pyknosis of ganglion cells.[3] Similar changes were observed in dogs killed after like treatment. Focal hemorrhages, disappearance of Nissl substance, and "acute swelling" of the ganglion cells have been noted in dogs[6, 10] and in guinea pigs and rats[10] after treatment with high frequency current. Rises of only 2° C. in rats, after similar exposure, were not followed by significant changes.[8] After a daily increase of temperature of from 4 to 6° F., also produced by high frequency current and continued over a period of several months, dogs showed some edema of the meninges and cortex, occasional hemorrhages and a powdery appearance of the Nissl substance.[10] The brain showed no evidence of irreparable damage.

Reports on the chemical changes in the blood associated with artificial fever have been to a certain extent confusing. Blood dilution has been found in human beings[5] while concentration has been reported in animals.[7, 8, 10, 11] Dogs show a rise in the nonprotein nitrogen,[7, 8] and variable changes in blood sugar.[8] No significant changes in calcium have been discovered in either human beings or animals.[5, 8] Inorganic phosphate was reduced as much as 25 per cent to 35 per cent in dogs at temperatures above 41.7° C.[8]

EXPERIMENTAL ANIMALS

Kittens and cats were the experimental animals studied. Since it was not always possible to know the age, this is not given in all cases. The weight may be taken as a rough index of the age and has been used here to divide the groups of animals. The kitten can be separated from its mother about the fifth or sixth week of life, and the weight at this time is usually from 600 to 800 gm., although we have had some who weighed as little as 350 gm. and others who weighed as much as 950 gm. When the age was not known, animals weighing less than 1000 gm. were con-

sidered kittens. If the age was known, those of less than ten weeks were considered kittens. Those weighing from 1000 to 1750 gm. were classified as intermediates, and those over 1750 gm. as adult cats.

METHODS

Three different methods* were used to induce fever in these experiments. The last method to be described proved most satisfactory but significant results were obtained with all three.

The first apparatus† employed was an ordinary bacteriologic incubator, altered by substituting for the solid shelf one of wire netting, below which was a pan to catch excreta. The animal was allowed to move about the interior at will. As removing the animal exposed it to a marked change in environment, the process of taking frequent temperature readings was discontinued after the first few experiments, and thereafter the temperature was taken only at the beginning and at the end of the experiment. The chief difficulty in this method was the inability to vary or check the temperature rise.

The second apparatus‡ consisted of a high frequency generator of 3 kw, with the field established between two large electrode plates. The filament voltage was kept at about 11 and the temperature rise regulated by varying the plate current. It was found that this adjustment could not be made sufficiently fine to produce any but gross changes in the speed of temperature rise. The animal was confined between the plates in a long, narrow, glass-sided cage with wooden ends, floor and top—the latter removable. The electromagnetic waves passed through the glass without difficulty except when the walls were covered with saliva.

Major difficulties were encountered with this apparatus, for if the animal voided or defecated, sufficient current was generated to produce sparking when the animal came in contact with the urine or stool. This difficulty was surmounted to a certain extent by having thin boards which covered the floor and could be dropped in whenever the original floor became soiled. Again, when there was excessive lachrymation, currents were set up in the tears, producing an irritative conjunctivitis. A large number of experiments had to be stopped before completion because of these difficulties, but some were finished successfully.

The third apparatus, a radiant heat chamber§ (Fig. 1), was constructed to expose the animal to heat waves from a wire coil. The chamber was built in the form of an elliptical cylinder of copper—used

*The three different chambers used in these experiments were all provided with ventilation, and in the first series there was a constant flow of air maintained by suction. The humidity was not controlled, but since the longer experiments, where any change would be greater, were negative for the most part, it is not believed that the humidity plays an important role.

†This apparatus was set up and the first series of experiments carried on with the help of Dr. J. G. Dusser de Barenne.

‡This apparatus was loaned to us by the General Electric Corporation through the courtesy of Dr. W. R. Whitney.

§This chamber was built by Dr. Herrington and Mr. Roody of the Pierce Laboratory of Hygiene.

because it affords maximum radiation with minimum absorption. At the upper focus of the ellipse was a heating coil which ran the length of the chamber, 3 feet. At the other focus was a removable slab of wood, perforated to allow the animal's legs to be inserted and secured with leather thongs. Its head remained upright and it could be offered fluids without difficulty. Since all waves arising at one focus of an ellipse will be reflected through the other, the greatest heating effect could be obtained from the coil. The electric input to the coil was the ordinary 110 volt D.C. A variable resistance in series with the coil permitted the

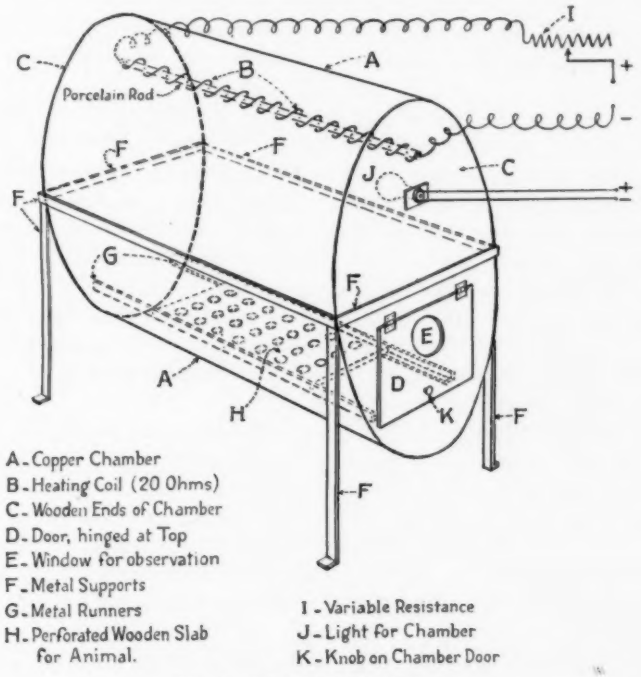

Fig. 1.—Radiant heat chamber.

amount of radiation to be changed at will. The temperature was taken by a clinical thermometer inserted in the rectum and kept there continuously by means of a wire spring. The thermometer was covered sufficiently so that the radiation did not affect it.

This method of raising the temperature of the animal was by far the most satisfactory of those tried, and it was found that a heating coil with a resistance of 20 ohms was sufficient to produce as rapid a rise as was desired. Through the window continuous temperature readings could be taken and the door opened when necessary without changing the temperature.

RESULTS

Several kittens exhibited minor twitchings, but the animal was not recorded as having had a convulsion until a typical generalized seizure was observed. The convulsion was of very sudden onset and the pattern similar in all cases. In the first two series the first manifestation was marked opisthotonos and generalized spasticity followed immediately by spasmodic jerking movements of all four limbs, head, mouth, ears, and eyelids. The pupils were maximally dilated throughout the seizure. The movements were often so violent that the body thrashed about wildly. In the third series the picture was modified because the limbs were restrained, but the general characteristics were unchanged. There was almost always defecation and urination coincident with the convulsion.

The duration of the seizures varied from a few minutes to over half an hour with the majority lasting about ten minutes. After the jerking movements ceased, recovery began with righting of the head, followed by the body and later by attempts to stand erect. In a few instances the animal was erect and walking around, although a little giddily, within half an hour after cessation of the convulsion. Some animals never got beyond the head-righting stage and died within a few hours. The experiments reported include all the animals whose temperature went up at least 3° C. during an experiment, since the production of a convulsion is the determining factor, and no convulsion occurred with a temperature increase of less than 3° C.*

No essential difference in the three groups is demonstrable either in the development of convulsions or the pathologic findings. Accordingly, all 82 experiments are distributed with regard to age group, temperature elevation, time interval, and results in Fig. 2, and all are grouped together in the subsequent analysis. Several factors must be evaluated as to their influence in the production of convulsions in these experiments, among the most important being age, height of rise, and speed of rise.

Age.—Division of results with regard to age of the animals is as follows:

	CONVULSIONS	NO CONVULSIONS	TOTAL
Kittens	26	28	54
Intermediates	4	12	16
Adults	2	10	12
Total	32	50	82

Even though the totals are small, the differences between the reactions of kittens and older cats are striking. Reasons for the lack of convulsions in many of the 28 kittens which did not develop them will appear later

*As the initial temperatures for cats of all ages varied from 37° to 39° C., the rise has been expressed in terms of increment rather than actual temperature level reached. The data have been analyzed using actual temperature levels, with essentially the same results as those reported.

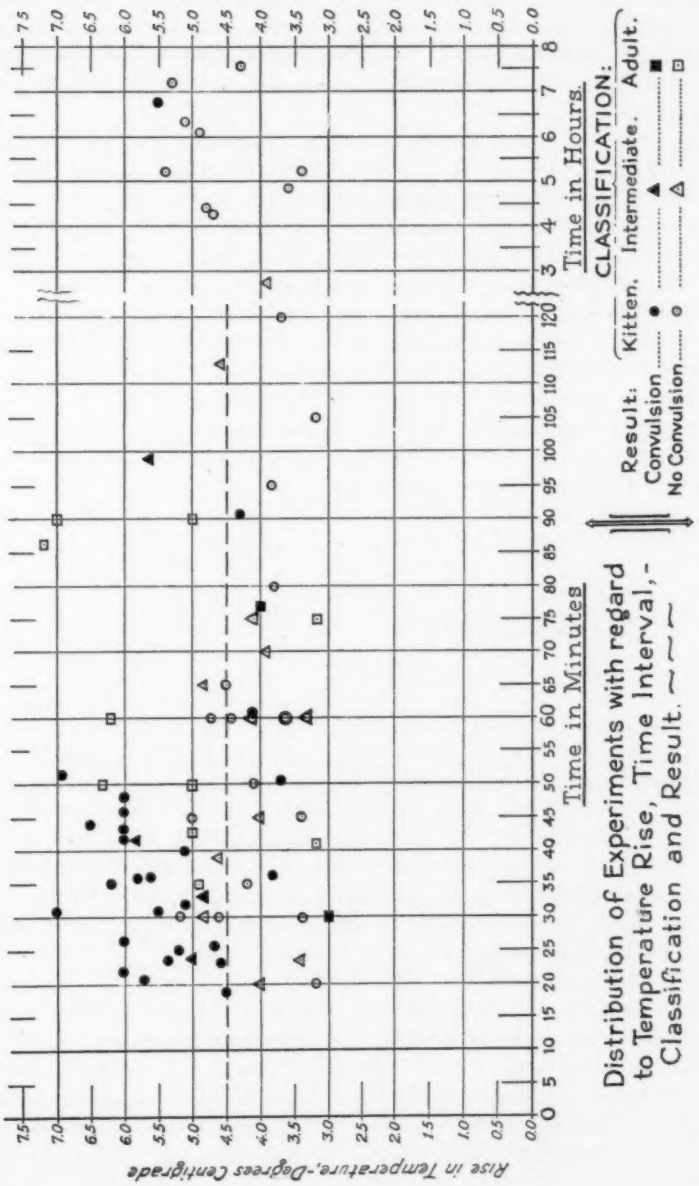
Rise in Temperature.-Degrees Centigrade
Time in Minutes
Time in Hours.
CLASSIFICATION:
Result: Kitten. Intermediate. Adult.
Convulsion ..... ● ..... ▲ ..... ■
No Convulsion ..... ○ ..... △ ..... □
Distribution of Experiments with regard to Temperature Rise, Time Interval, - Classification and Result. ~~~

Fig. 2.

in the analysis. Moreover, in the third series when the temperature was raised rapidly and uninterruptedly, a convulsion was produced *every* time in 9 kittens, as against twice in 5 adults. The fact that a similar trend can be seen in each of the three series supports the conclusion that convulsions as a result of fever occur more frequently in immature than mature cats.

Height of Rise.—It is obvious from Fig. 2 that the higher the temperature, the more frequent is the occurrence of convulsions. A rise of 3.7° C. was the lowest with which a kitten had a convulsion.* The interrupted line at 4.5° C. of rise shows that above this level 11 kittens did not have convulsions (of which 6 were heated slowly, v.i.) while 23 did. This may be contrasted with 8 adults, none of which had convulsions. It is apparent that higher temperature not only facilitates the production of convulsions in kittens but also brings out more sharply the discrepancy between their reactions and those of adults.

Speed of Temperature Rise.—In twelve experiments on kittens the temperature rise was made more gradual and prolonged. In this group temperature increases which, when induced rapidly, were usually accompanied by convulsions, brought about this result in only one of ten experiments. Setting an arbitrary dividing line at 100 minutes, the following tabulation is arrived at for the experiments on kittens:

	CONVULSIONS	NO CONVULSIONS	TOTAL
Under 100 minutes	25	17	42
Over 100 minutes	1	11	12
Total	26	28	54

The difference is made more striking by further examination of the 17 kittens which did not have convulsions in the group under 100 minutes and of the one who did in the other group. Of the former, one in the first series and seven in the second series had temperature increases of less than 3.7° C., the lowest level at which any kitten had a convulsion. In the one experiment from the third series the speed of rise was retarded, designedly, as illustrated in Fig. 3 (Cat 9). The one animal which had convulsions in the group heated over 100 minutes was Cat 18, third series, which is discussed below.

A further contrast is brought out by consideration of the final condition of the animals which did not have convulsions. In the "long" group all kittens were either dead or dying at the conclusion of the experiment, while in the "short" group all except one recovered. This may be taken to indicate that in the "long" group the maximum effect from fever had been obtained, while in the "short" group, on the contrary, the possibility exists that further temperature increase might have induced a convulsion in those animals which did not have a seizure.

*The single observation of a convulsion in a full-grown cat after a temperature elevation of only 3° C. is a little surprising since this is almost a degree less than the lowest rise associated with a convulsion in a kitten.

Several examples of the temperature curves are shown in Fig. 3. Cats 1 and 12 are instances of uninterrupted rise, and it is seen that the curve approximates a geometrical progression. This tendency was constant through all experiments of this type. Cat 1, a kitten, had a con-

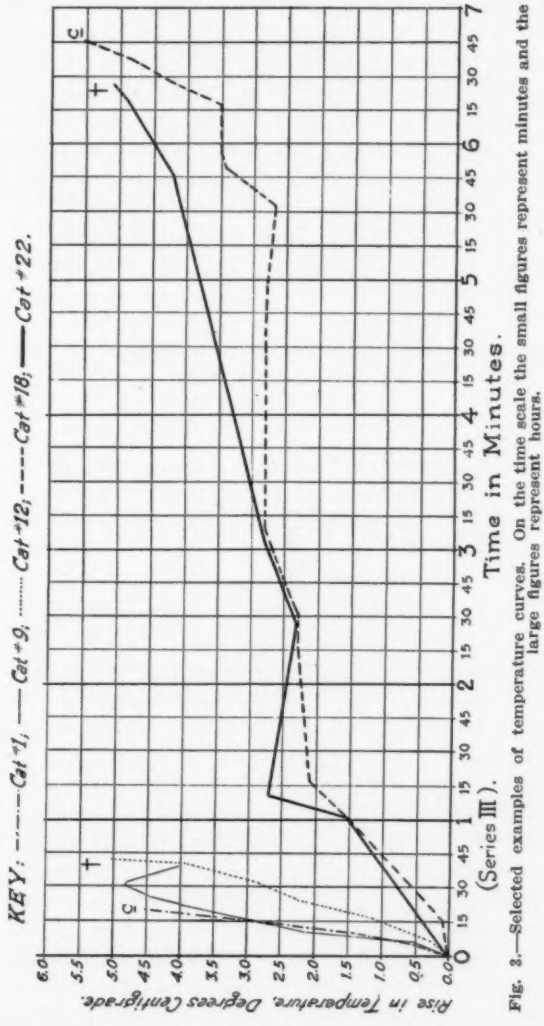

Fig. 3.—Selected examples of temperature curves. On the time scale the small figures represent minutes and the large figures represent hours.

vulsion after a temperature rise of 4.5° C., and recovered completely. Cat 12, an adult, died after an increase of 5° C. without developing a convulsion.

After an initial rapid rise during the experiment on Cat 9, a kitten, the heat input was reduced gradually and the temperature followed the

course as illustrated. Although the highest temperature reached was well in the zone where a convulsion might be expected, it is possible that the retardation of the latter part of the rise may have been the factor which prevented its occurrence. It must be remembered that this experiment was in the third series where a convulsion occurred in every experiment on a kitten where the temperature rise was uninterrupted.

The other two curves illustrate the difficulty in producing a slow smooth rise. Although the increase in Cat 22, a kitten, was far from smooth, it was comparatively steady. The final temperature reached exceeded the highest levels in the "short" experiments shown, but the animal died at the conclusion of the experiment without developing a convulsion.

The curve of Cat 18, a kitten, is very interesting, since it is the only one showing a convulsion in the "long" group. The latter part of the rise was much more rapid than in Cat 22 and was of an order approaching the type of rise found in the "short" experiments. This fits in with the finding that the rapidity of temperature increase is the determining factor in the production of convulsions.

PATHOLOGICAL FINDINGS*

Nine brains were examined; all were from the first series except Cat 17, which was in the third series. Necropsy was done immediately after death. None showed any abnormality macroscopically. The specimens were fixed in 95 per cent alcohol, embedded in parlodion, and stained with toluidin blue by the Nissl technique.

The results of a sharp rise in temperature followed by a convulsion were demonstrated in Cats 3 and 4, kittens (Fig. 4). Cat 3 died 20 minutes after the second of two convulsions occurring with a rise of 6.4° C. in 71 minutes. Cat 4 died three hours after a convulsion following a rise of 5.1° C. in 40 minutes. Many ganglion cells showed deep blue clouding of the cytoplasm with obliteration of the Nissl bodies. Other ganglion cells, particularly in the superficial cortical layers, were extremely pale and devoid of nuclei. There was a questionable diffuse disappearance of nerve cells in the first three cortical layers.

No evidence was found of a glial reaction. The changes found in the cortex were also found in all the cerebral nuclei.

Cat 6, an intermediate, had a rise in temperature of 5.6° C. in one hour and thirty-nine minutes. This cat developed marked convulsive twitchings but no generalized convulsion, and died twenty minutes later. The brain showed the same changes as in Cats 3 and 4, although in addition the cell processes were stained intensively for long distances.

Cat 2, an adult, was autopsied immediately after a rise in temperature of 7° C. without a convulsion. The brain showed findings similar to those in Cats 3 and 4 but to a less degree.

*These were done in the Laboratory of Pathology, division of Neuropathology, under the direction of Dr. Harry M. Zimmerman, who made the examinations and interpretations.

Cat 17, kitten, third series, was autopsied immediately after a slow rise of 5.3° C. in seven hours and eleven minutes. The ganglion cells presented a very unusual appearance (Fig. 5). The cell bodies were markedly shrunken and devoid of tigroid substance. The nucleus occupied almost the whole of the cell, was pale in color and had a minute

Fig. 4.

Fig. 5.

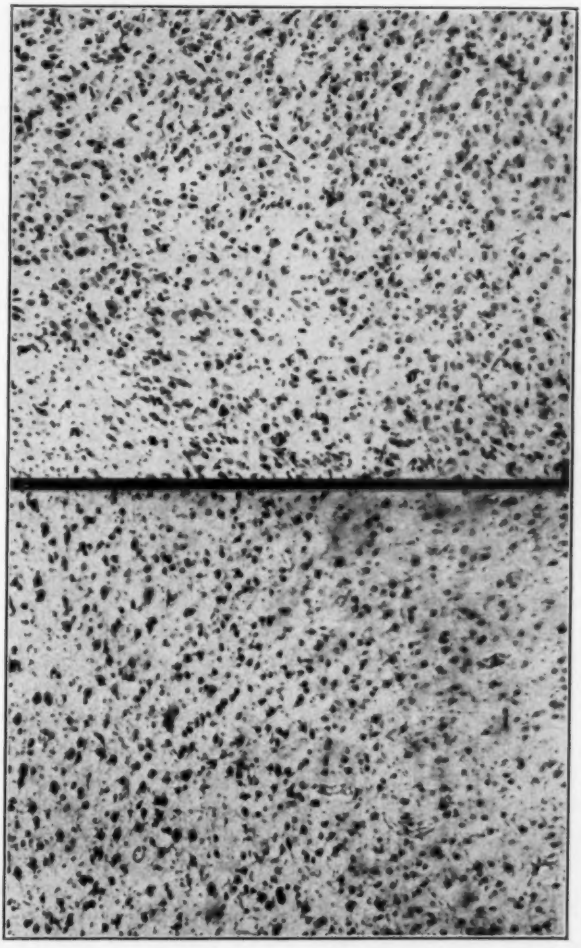

Fig. 4.—Section of brain cortex from kitten which had rapid temperature rise.
Fig. 5.—Section of brain cortex from kitten which had slow, prolonged temperature rise.

centrally placed nucleolus. The cell processes were short, chubby, and hyperchromatic. These changes were present also in the basal ganglia, medulla, and cerebellum.

Three animals were killed after a recovery period. Cat 9, a kitten, had its temperature raised 3.7° C. in fifty-one minutes, had a severe

convulsion, and recovered completely clinically. When killed eleven days later, the brain showed no changes at all.

Another kitten, Cat 8, at the time of the first experiment had a sharp rise followed by a convulsion and recovery, and two subsequent heatings at intervals later without convulsions. This cat seemed all right clinically. At autopsy four months later the ganglion cells showed diffuse chromatolysis with poorly stained Nissl apparatus. No other changes were noted.

A third, Cat 10, had a rise of 6.2° C. in one hour without a convulsion and recovered with the aid of an hypodermoclysis. Subsequently the animal was sluggish and was killed four and one-half months later. The brain showed the same changes as those in Cat 8 but to a greater degree.

That heating produces alterations in the ganglion cells has been noted elsewhere as well as in this series. The type of change in the one specimen from a slow prolonged heating, particularly the marked shrinkage of the cell, has been observed but rarely by Dr. Zimmerman.* One cannot distinguish, from a standpoint of pathology, between the animals having convulsions and those having none, nor is any difference demonstrable between the brains of kittens and adult cats. In one instance the brain recovered completely after a single insult and convulsion, but in two others definite changes were found several months after, in one case, an extreme temperature rise, and in the other, repeated rises.

DISCUSSION

These experiments indicate that in a high percentage of cases hyperpyrexia in kittens is followed by convulsions and that adult cats are much less likely to react in this manner. Furthermore, it appears that a rapid elevation of temperature is more likely to produce a convulsion than a slow rise. Just how much the increase must be varies with the individual animal. No convulsions were produced with an increase of less than 3° C., and an increase as high as 5.2° C. failed to produce a convulsion in one instance. With the radiant heat chamber it was possible to produce a convulsion every time, when subjecting kittens to rapid heating.

What is the mechanism by which the increased temperature produces a convulsion, and why is it operative in younger animals to so much greater an extent? Pathologic changes have been demonstrated in the ganglion cells of the brain and chemical studies† have shown that water leaves the brain cells for the intercellular spaces, but in both instances the findings appear to be related to the hyperthermia rather than the convulsions.

*Striking confirmation of this observation has been made by Yannet and Darrow,[18] who, in studies on these and other cats treated as in the third series, found that water shifted from inside to outside the cells after a rise in temperature. No differences related to the convulsions were noted.

†In five animals, of which four had convulsions, blood sugar was determined by Somogyi's modification of Hartmann's method, and nonprotein nitrogen by Nesslerization of the Folin-Wu filtrate. The sugar varied from 200 to 300 mg. per cent. The nonprotein nitrogen was elevated to 80 and 100 mg. in two animals, one of which had a convulsion, and in both of which hyperthermia persisted for about six hours.

The studies of Langworthy[9] in cats, on the relation of function to myelinization, indicate no reason from the standpoint of embryology, for a heightened susceptibility of the immature nervous system to convulsions. If anything, the converse would be expected, for the progress of myelinization, whether cause or effect, is concomitant with *increase* in function. It is possible that an incompletely integrated nervous system may respond with a convulsion to a situation which would not produce one in an adult. The ability to have a convulsion at all would be dependent on a certain minimum development of control of voluntary muscle. Bary (quoted by Langworthy) was unable to produce epileptic seizures by faradic stimulation of the cortex in kittens under two months of age. It is of interest to note that in the present work two of the animals in the second series who failed to have convulsions were litter mates who were very small, and that a third member of the litter had a convulsion only with a rise of 6.5° C. (Cats 11, 12, 13).

In considering the implications of this work for human infants, one must keep in mind the difficulty of comparing animal and human reactions. The conditions are not similar to those existing when a child becomes ill, and the temperature rises are, in many instances, of a magnitude very rarely seen in children. These difficulties are of no concern in studying the phenomenon experimentally, for the chief interest lies in the comparative results in immature and mature animals. It is true that these experiments are consistent with the clinical impression that the convulsions which appear in infants with the onset of an acute febrile disease may be produced by the fever alone without regard to the type of infection or the characteristics of the infecting organism.

SUMMARY

Kittens subjected to rapid rise in temperature have convulsions in a large percentage of cases.

Adult cats under similar circumstances have convulsions much less frequently.

When the temperature rise is slow and gradual, convulsions are rare even though a considerable elevation is reached.

Neuropathological changes have been found to be different for rapid and slow elevation, but no changes peculiar to convulsions have been demonstrated.

No explanation for the mechanism of the convulsions has been found.

SUMMARY OF PROTOCOLS

SERIES 1. Incubator for rapid heat induction
Total Animals: 10 Total Experiments: 16

	CONVULSIONS	NO CONVULSIONS	TOTAL
Kittens	3	3	6
Intermediates	1	4	5
Adults	0	5	5
Total	4	12	16

SERIES 2. High frequency current

A. For rapid heat induction
Total Animals: 20 Total Experiments: 34

	CONVULSIONS	NO CONVULSIONS	TOTAL
Kittens	13	13	26
Intermediates	0	6	6
Adults	0	2	2
Total	13	21	34

B. For slow heat induction
Total Animals: 4 Total Experiments: 4

	CONVULSIONS	NO CONVULSIONS	TOTAL
Kittens	0	4	4
Total	0	4	4

SERIES 3. Radiant heat chamber

A. For rapid heat induction
Total Animals: 17 Total Experiments: 17

	CONVULSIONS	NO CONVULSIONS	TOTAL
Kittens	9	0	9
Intermediates	3	0	3
Adults	2	3	5
Total	14	3	17

B. For slow heat induction
Total Animals: 10 Total Experiments: 11

	CONVULSIONS	NO CONVULSIONS	TOTAL
Kittens	1	8	9
Intermediates	0	2	2
Total	1	10	11

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HYPERGENITALISM IN CHILDREN

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A BOY exhibiting precocious sexual development with excessive urinary prolan excretion was studied, in whom treatment utilizing the mechanism of antagonism of hormones and also roentgen ray therapy were used.

INTRODUCTION

Precocious sexual development, it is stated, is usually due to hypergonadism, adrenal cortical hyperplasia or tumorous formation, and pineal gland tumors.[1]

Hypergonadism[2] in the male, it is generally conceded, is manifested by premature ossification and epiphyseal closure, spermatogenesis, and unusual physical strength. Tierney reported three boys, two of whom were mentally backward, with somatic and genital overdevelopment, all showing premature ossification. No statement was made about spermatogenesis. He attributed the condition to hypergonadism. Tumors of the testes, likewise of the prostate, are rare before puberty. Testicular tumors metastasize very readily and excessive urinary prolan is of diagnostic significance. Tumors of the gonads are far more common in girls and precocious puberty due to granulosa-cell growths has been reported with recession of the sexual development following operative treatment.

Adrenal cortical tumors may cause testicular hyperfunction. Among children and adolescents they are about five times as common in girls as in boys.[3] The anthropometric measurements are usually normal. The mentality may be normal, although mental precociousness as well as idiocy have been recorded.

Pineal tumors producing precocious puberty occur practically only in boys and sooner or later are characterized by general symptoms of cerebral tumor followed by local signs. The experimental evidence of the function of the pineal is not conclusive. Pineal extirpation experiments are controversial, and clinical cases can be adduced to support the various views held. The mentality may be normal, precocious, or dull.

Hyperpituitarism, which presumably may produce this phenomenon, occurs predominantly in males and is characterized by a general skeletal overgrowth especially of the long bones. It may be caused by overproduction of the growth hormone generally as a result of a tumor of the eosinophilic cells.

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Reuben and Manning in their extensive review of the subject of precocious puberty state that no case of primary pituitary gland dysfunction was proved either at operation or post mortem. In a recent personal communication to McCune and Bruch,[4] Reuben said that continued familiarity with the literature gave him no reason for modifying his original thought. Laurie asserted that hypergenitalism never occurs in pituitary lesions of any kind.

Wolf states that a tumor of the pituitary involving the basophilic cells may result in hyperorchidism. It has been suggested that theoretically the gonadotropic hormone of the anterior pituitary may cause premature sexual stimulation.[5] Possibly the pathogenesis of some of the cases of hypergenitalism can be explained by this mechanism.

Bland and Goldstein[6] in a recent study of pituitary basophilism (Cushing's syndrome), which produces sexual hypofunction in both sexes, reviewed the 42 cases verified at operation or post mortem. The ages of the patients, of whom ten were males, varied from 11 to 65 years. Hyperplasia and hypertrophy of the adrenal cortex alone or with definite adenomatous formation were frequent. The author's patient, a female aged 20 years in whom prolan and estrin determinations were negative, improved after deep irradiation therapy to the pituitary.

Wright[7] reported the youngest patient with pituitary basophilism, a male of 11 years. This boy exhibited obesity of the neck, face and trunk, also hypertrichosis of the latter two. Lineae atrophiae were present on the abdomen. The pubic hair was abnormal, and the external genitals were small. The testes were descended. There were no intracranial symptoms. X-ray plates of the kidney area revealed no calcification, and the wrists and the sella turcica were negative. Decalcification was present in the anterior and posterior clinoid processes. The urine was negative; some polycythemia was present; the basal metabolic rate was –18 per cent; and the blood pressure, 154/110.

The patient died after an appendectomy and a basophilic adenoma was found at post mortem. The adrenals, thyroid, and parathyroids were normal. The pineal was somewhat enlarged.

The following less frequently considered groups may also be responsible for the production of hypergenitalism:

A. The cerebral group in association with lesions of:

1. The hypothalamus
2. Tumors of other portions of the brain
3. Hydrocephalus (chronic) and encephalitis

B. The primary constitutional group of Orel[8] of which familial occurrence may be listed as a subdivision.

A. Lesions in the hypothalamus as well as in other parts of the brain, hydrocephalus alone or associated with the latter, and encephalitis may

produce sexual precocity through the hypothalamic-hypophyseal mechanism with no associated lesions in the endocrine glands.

1. Vickers and Tidswell[9] studied a boy of 8 years whose sexual development was that of an 18-year-old. The penis was large at birth and grew rapidly thereafter. Hair appeared at the pubis at 3½ years, in the axillae at 4, on the lip at 6, and at this age the voice became deep toned. The child had emissions, no sexual desires, was mentally backward and exhibited spells at which time his behavior was uncontrollable. There existed no hydrocephalus or other evidence of intracranial involvement. The suggestion was made that this boy presented symptoms of hyperfunction of the basophilic cells without involvement of other elements of the anterior lobe. Hormonal studies were not made and spermatogenesis was not recorded.

The patient came to autopsy and a nonobstructing tumor was found which was the size and shape of a walnut occupying centrally the floor of the third ventricle and projecting freely into it. The tumor apparently developed in a manner causing no serious disturbance of the surrounding parts. Histologically the growth was an astrocytoma with no cyst formation.

The pineal, thymus, adrenal and thyroid were macroscopically and microscopically negative, as was also the pituitary, which revealed no excess of basophilic cells. The gonads, normal grossly, were not preserved for microscopic section.

2. LeMarquand and Russel[10] reported a boy 4 years and 10 months old who showed great strength, abnormal appetite, ceaseless activity, and most unusual symptoms of sexual precocity. An abdominal exploration with the removal of the right suprarenal was done because the picture corresponded to one of adrenal virilism. Later the right testis was removed. Neither operation was followed by change.

The boy came to necropsy and the only significant finding was a circumscribed tumor attached to the right corpus mammillare and to the left side of the tuber cinereum. Apparently this tumorlike mass at the base of the brain was the only pathologic change to which the condition could be ascribed. There was no internal hydrocephalus. The adrenals, pineal, thymus, pancreas, thyroid, and parathyroids were normal. Serial sections of the pituitary and hypothalamus showed no abnormalities. Sperms were found in the lumen of the testes.

3. A number of reports have appeared of physical and sexual precociousness associated with hydrocephalus in boys and girls, and at post mortem the adrenals, testicles, pineal and hypophysis were normal.[11] Dorff recently presented a clinicopathologic study of sexual precocity with hydrocephalus in a report of two female children with a post-mortem examination of one. Krabbe's boy with precocious puberty in addition to an internal hydrocephalus also had lesions of tuberous sclerosis in the brain. Spermatozoa were found in the testes.

B. Rush and co-workers[5] reported a family falling into the primary constitutional group in which no secretory or physical abnormality was discovered to explain the phenomenon. In the discussion they quote a number of instances of familial occurrence of pubertas precox.

In the family studied there were eight instances in four generations; there was no known involvement of females. In addition to the father and two sons, there was a history of precocity in two great-uncles, one distant male cousin, a paternal grandfather, and a great-grandfather.

At the time of study the ages of the father and two sons were 33, 8, and 5 years, and the unusual sexual development began respectively at 5, 1½, and 3 years. The body measurements of the older boy were like those of a 16-year-old, those of the younger son corresponded to an 8-year-old. The wrist bone age of the former was 17 and of the latter 12. The older boy had acne of the face, emissions, and masturbated. The mental age of both was normal. The question of spermatogenesis was not discussed.

REPORT OF CASE (FIG. 1)

D. M., born July 15, 1927, was first seen at the age of 9½ years because of unusual sexual development. The penis, which began to grow large at the age of 5 years, continued to do so until the age of 7 years, when growth seemed to stop, and then the process was resumed. Pubic hair appeared at 7 and axillary hair at 9 years. There was no history of nocturnal emissions, masturbation, or interest in the opposite sex, although erections were present. When the boy started school at 6 years, he was found mentally retarded; a recent mental test revealed similar findings (Binet 81; performance test, 78; grade achievement, 2nd).

He was a normal, full-term baby weighing 7½ pounds at birth. The physical development was apparently normal. Neither illness nor any other predisposing factor played a role in his physical or mental condition. At the age of 6 years he had a head injury which caused pain for about two weeks, but there was no associated vomiting, convulsions, or unconsciousness. The family history was negative for endocrine and nonendocrine disturbances. The mother, 43 years old, the father, 38 years old and one other child, a younger boy, were in good health. Other than painful erections at times and some degree of sensitivity over his condition, there were no complaints.

The boy possessed no unusual muscular strength, was nohow obese, and his body measurements at the initial visit corresponded to the growth of an early 11-year-old. Fifteen months later the body measurements were approximately like those of a boy 16½ years old.* Other than the face, which exhibited a profuse eruption of simple

*Measurements

At time of first visit (9½ years)	*Fifteen months later* (after 60 injections of estrin and 10 x-ray treatments).
Weight: 42.9 kg.	Weight: 54.5 kg.
Height: 154.25 cm.	Height: 161 cm.
Circumference of head (occipitofrontal): 54 cm.	Circumference of head (occipitofrontal): 55 cm.
Circumference of chest: 70 cm.	Circumference of chest: 80 cm.
Circumference of abdomen: 59 cm.	Circumference of abdomen: 64 cm.
Span: 156.5 cm.	Span: 165.5 cm.
Pubis to sole: 77.125 cm.	Pubis to sole: 81 cm.
Pubis to vertex: 77.125 cm.	Pubis to vertex: 80 cm.
	Bisacromial: 22 cm.
	Right and left midthigh: 45 cm.
	Right and left midcalf: 32 cm.
	Right and left midarm: 24 cm.

lentigo on the nose and adjacent portions of the cheek and forehead in addition to small comedones and acne pustules, and the genitals, the physical examination did not reveal any special findings.

Genitals.—The penis (14 cm. in unerect state) was of adult size; the prostate, which was firm, and the epididymis were slightly smaller than those of a grown man. The right vesicle was palpable, but the left was not. The testes were smooth, not tender, and contained no nodular masses. The right measured 4 by 2.5 cm. and the left 3.5 by 2 cm. Massage of the prostate produced a normal appearing fluid, and,

Fig. 1.

microscopically, prostate cells were absent. Vesicle massage revealed a lipoid fluid containing no sperms. The urine voided following massage was likewise negative for spermatozoa. The above findings remained essentially the same following therapy.

LABORATORY AND OTHER DATA

Eyes.—Fundi, negative; visual fields grossly normal; color perception normal.

Roentgen Ray Studies.—Sella turcica negative. Films of the wrist at initial visit and after 15 months showed no precocious ossification or premature union of epiphyses. Plates of the extremities revealed no areas of osteoporosis. Films made

of the abdomen showed no abnormal calcification or other pathology. Preliminary film of the urinary tract was negative. Films made at intervals of 10 and 30 minutes after injection of iodine compound showed the urinary tract lumen outlined by opaque medium. No abnormalities were present.

The blood pressure was 125/85 on two occasions; the electrocardiogram was normal.

Mantoux test, 1/1000, negative. Blood count: 4,750,000 red blood cells; 5,400 white blood cells; hemoglobin 75 per cent. Differential: 54 leucocytes, 41 lymphocytes, 5 monocytes. Spinal puncture findings negative. Kahn test negative. Intradermal injection of antuitrin-S raised a wheal.[12] Creatine excretion was normal. Cholesterol, 140; fasting blood sugar, 91. After ingestion of glucose the readings were: 93, 100, 101.

Basal Metabolic Rate.—Surface area, 1.39; calories per square meter per hour, 51.0; normal based on surface area, 50; basal metabolic rate, +2 per cent.

Encephalography.—No abnormalities noted.

Hormonal Assays.—A positive Friedman test was present on entrance, indicating excessive amounts of prolan.* This test remained positive after theelin administration and irradiation of the hypophysis. The assay was repeated by the Zondek precipitation method and a minimum of 400 mouse units was found.†

No determinable amounts of estrin were found at the time of entrance nor after 60 injections of theelin.

Androgen excretion studies in urine were not performed.

Treatment included (1) 12,000 rat units (60,000 international units) of estrogenic substance and (2) deep irradiation therapy to the pituitary (570 R.).

COMMENT

Our patient presents a diagnostic problem to which no conclusive solution can be offered. In a sense the diagnosis must be conjectured; possibly only autopsy can give the final answer. We must bear in mind the interrelationship of the endocrine glands, therefore in any pathologic condition the involvement of one affects all others and the determination as to which is responsible is attended with great difficulty.

In our patient adrenal and pineal involvement can readily be ruled out. The negative results after repeated abdominal examinations, normal visualization of the genital tract and the absence of calcification in the kidney area argue against adrenal pathology (perirenal air administration was not attempted). The absence of any intracranial involvement and the lack of progression over a long period are against pineal etiology.

The absence of spermatogenesis on repeated occasions, as well as the absence of premature ossification and epiphyseal closure, is against hypergonadism as this is usually conceived. The normal consistency of the testes (no change in 14 months) and the absence of metastases rule out testicular neoplasms. Biopsy of the testes, it was felt, was not indicated.

*The Friedman test (Reactions II and III) is positive in the first half of pregnancy when 2,000 to 6,000 gonadotropic hormone units per liter of urine are found, although amounts up to 50,000 units may be obtained. Normally in children little if any gonadotropic factor is found; in young adults from 4 to 19 mouse units have been assayed.

†Zondek, B.: Die Hormone des ovarium und des hypophyse Vorderlappin, Berlin, 1931, Julius Springer.

There is little evidence for postulating hyperpituitarism except to restrict this phenomenon to excessive function of the basophilic cells. In Wright's case of pituitary basophilism in a preadolescent boy, the usual manifestations associated with Cushing's syndrome were found. Our boy had neither obesity, osteoporosis, hypertension, nor polycythemia. The only evidence for the presumed hyperfunction of the basophilic cells is the excessive amount of prolan, which was not determined in Wright's patient. It is to be emphasized that precocious puberty is not caused by pituitary basophilism. Excessive prolan excretion establishes the pituitary as a primary factor, as seems most likely on theoretical grounds. Little is known of the pituitary in hyperorchidic conditions. In the present state of knowledge and because of the few studies in similar conditions, comparisons are not feasible.

In this connection the production of changes simulating premature puberty by the use of anterior pituitary-like principle of pregnancy urine in three male children undergoing treatment for cryptorchidism is interesting.[13] There occurred an increase in the size of the penis, scrotum, and prostate, growth of pubic hair, frequent erections and a change in the pitch of the voice, but no sperms. The testes, however, showed very little change in size. It seems as if in our boy, who exhibits excessive amounts of urinary prolan, nature performed what quite large doses (60,570; 34,720; 55,020 units) of antuitrin-S administered parenterally accomplished in other boys.

The question of an hypothalamic tumor producing sexual hyperdevelopment with no endocrine involvement without intracranial symptomatology must be borne in mind. Apparently a rather large slowly growing astrocytoma can produce a picture as seen in our boy, with no cerebral symptoms, through involvement of some of the diencephalic nuclei. However, the encephalogram was negative in our patient. The patient of Vickers and Tidswell, in whom no hormonal assays were done, offers evidence that the hypothalamus has a relation to certain fundamental functions as sexual development. Either alone or in conjunction with the pituitary it plays a role through the diencephalic-pituitary mechanism. In destructive lesions of both of these structures sexual atrophy occurs. In this case sexual hypertrophy was present, and the lesion was assumed to have been "irritative."

Kraus[14] has written on the role of increased intracranial pressure in relation to disturbances of the pituitary gland. He stated that in patients with neoplasms of the brain or meninges or patients with chronic internal hydrocephalus associated with chronic increase in intracranial pressure the anterior lobe of the pituitary is either underactive or overactive depending on the particular changes in the hypothalamic region. In his patients with increased intracranial pressure the ovaries showed a considerable percentage of microcystic degenera-

tion. A portion of these showed an increased amount of follicle-stimulating component, which was also exhibited by some of the males.

Wolf discusses the situation as regards testicular involvement. If tumors of the testicles are of the secretory type, then definite hyperorchidism may result. If, however, the tumor is a carcinoma affecting the germinal epithelium, eunuchoidism may result. The author stresses the importance of keeping this in mind as it may explain many discrepancies of the different effects of tumors on endocrine glands.

As far as the constitutional type there was no known family history of endocrinopathy in our boy; nevertheless, the possibility that the picture seen may be the result of defective germ plasm must be considered. The report of Hecker and Warren[15] on girdle type of adiposity among mentally deficient males is interesting in this respect. The boy of 8 years reported by Rush and co-workers, had acne; so did ours. At one time in our boy these lesions were interpreted as adenoma sebaceum which is interesting in view of Krabbe's report of precocious puberty in which there was an associated tuberous sclerosis. The prolan determinations in the above boys were negative, but they had positive excretion of male sex hormone which ordinarily does not occur before the age of 10 years.

The use of female sex hormone to counteract the excess prolan was suggested by Zondek's experiments,[16] in which the follicular hormone was found to interfere with the physiologic effect of the secretion of gonadotropic hormones of the anterior pituitary. Female sex hormones injected into the male rabbit produced disappearance of the scrotal sac, decrease in size of the penis, retention of infantile testes, and inhibition of sperm formation.

Moore[17] on the basis of experimental work in his laboratory developed and suggested a mechanism of reciprocal interactions between the gonads and the pituitary. The anterior lobe of the pituitary gland regulates the activity of the sex gland. Removal of the pituitary is followed by cessation of germ cell production and hormone secretion. The injection of estrogenic substance into normal males causes failure of both germ cell production and hormonal secretion. The pituitary is rendered less potent by the administration of gonadal hormones. (This has been carried out clinically in acromegaly.[18])

Our patient received 12,000 units follicular hormone without affecting the prolan excretion. Assay of the urine after these injections revealed no determinable amount of estrogenic substance. In a gynecomastic patient who showed abundance of prolan in the urine and to whom 60 injections of male sex hormone* were given, the excessive urinary gonadotropic output was not affected.[19]

*Hydrosoluble fraction from spermatic gland plus liposoluble principle from interstitial gland (144 gm. of fresh gland) and testosterone propionate (210 mg., approximately 10,500 international units).

The studies of Frank, Goldberger, Salmon and Felshin[20] are interesting in this connection. They found in their work in amenorrhea that at least 200,000 rat units (1,000,000 international units) were necessary to reduce excessive excretion of gonadotropic substance, while in one case 400,000 units failed to produce this result. In view of this, perhaps the persistence of the excessive gonadotropic substance after the 60 injections of estrin in our patient was due to the insufficient amount used. Furthermore, in their studies they showed that when the gonadotropic factor was either in excess or deficient, the estrogenic excretion could be diminished, normal, or excessive.

The treatment by irradiation to the pituitary was successfully utilized in Bland's patient with basophilic adenoma. McCullagh and Cuyler[21] found, in cases of pituitary tumor in which the Friedman test was positive, diminution in urinary prolan following radiation therapy to the pituitary. Lawrence and his co-workers[22] by irradiating the pituitary in rats produced retardation of growth and inhibition of ovarian activity. No permanent changes, however, were produced in the irradiated gland. X-ray therapy to the testes in our patient did not seem indicated.

SUMMARY

A study is recorded in a mentally retarded boy with precocious sexual development exhibiting neither spermatogenesis, premature ossification, nor epiphyseal union.

Hydrocephalus was not present. An intracranial involvement possibly of the hypothalamus must be borne in mind. The encephalogram exhibited no pathologic findings.

The similarity of our boy, who exhibited excess excretion of prolan, to the children receiving large amounts of gonadotropic substance is interesting.

That the manifestations of the hypergenitalism may be the result of a defect in germ plasm also producing the mental defect is possible.

In addition to a discussion of differential diagnosis, therapy is suggested.

Acknowledgment is made to Dr. Hartung and Dr. Wachowski for x-ray therapy; to Dr. Stulik of the Cook County Hospital, where the patient was first seen; to Dr. Wade for creatin determinations; and to Dr. Rezek for assistance in interpreting hormone reactions.

Note.—Since submitting this article for publication I have had an assay on the boy for the male sex hormone by A. T. Kenyon, M.D., of the University of Chicago Clinics, who sent me the following report:

"Your boy showed the presence of 55 international units of androgens per liter of urine. There were 4.08 liters, but measurement of the twenty-four-hour specimen was unfortunately neglected so that I cannot give you the values per day. This 55 international units is a normal value for an adult male."

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ACUTE INFECTIOUS DUODENITIS (INFECTIOUS JAUNDICE)

Report of 76 Cases

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ALTHOUGH jaundice is fairly common in children, widespread epidemics are of rather infrequent occurrence. It is our purpose in this paper to describe the clinical features of an epidemic of 76 cases of acute infectious duodenitis with and without jaundice. We have selected the term acute infectious duodenitis in preference to acute infectious jaundice because almost half of the cases that we encountered did not have jaundice. The clinical picture and course of the disease, with the exception of jaundice, was quite similar in all of these cases. We feel that the etiology and essential pathology of both the jaundiced and nonjaundiced cases were the same. This was particularly evident in those cases where several members of a family became ill; sometimes one or two members of a family would be jaundiced whereas the others developed a similar syndrome with the exception of the jaundice.

EPIDEMIOLOGY

Beginning on Sept. 20, 1937, we encountered an epidemic of cases that presented the following clinical picture: sudden onset with abdominal pain, vertigo and headache, followed by nausea and frequently by vomiting; over half of the patients developed jaundice within two to five days. The disease occurred chiefly in children between the ages of 3 and 16 years. The epidemic reached its height about November 1. There were, however, periods of a few days to a week characterized by a marked decrease in the number of cases and followed by periods during which more cases occurred. The epidemic lasted through the months of December and January and has not yet reached its end at the time of the present writing (Feb. 15, 1938). There was no question about the high degree of contagiousness as three or four members of one family would frequently become affected. The cases could be traced from one district or community to another in a very definite fashion.

The incubation period varied from fourteen to twenty-one days. It was possible to determine the approximate incubation period by noting the time that elapsed between the appearance of symptoms in various members of one family.

CLINICAL FEATURES

There were two types: With jaundice and without jaundice.

Jaundiced Cases.—This group of 40 patients presented the following symptoms. The onset was sudden with epigastric pain, headache, and vertigo; nausea, or nausea and vomiting usually followed the pain in a

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few hours or a day. Diarrhea, weakness, anorexia, sore throat, and low grade fever were frequent symptoms. Jaundice appeared within two to five days from the onset. Many of these patients presented a picture of collapse when first seen; this was usually accounted for by the persistent vomiting. The temperature varied, as a rule being low grade; sometimes the temperature was normal, and in a few of the severe cases there was a high fever. There did not seem to be any definite relationship of the disease to leucocytosis: the leucocyte count varied from 6,450 to 15,000. The sedimentation rate was usually normal or slightly

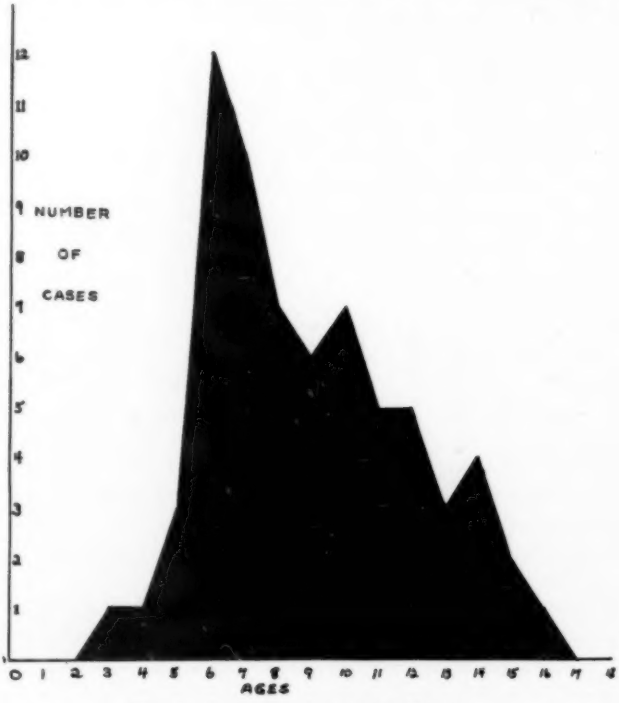

Fig. 1.—Chart showing age incidence.

increased. Fragility test was normal. The urine showed bile. The van den Bergh test was immediate direct positive in the severe cases and delayed direct in the milder ones. The icterus index varied from 12 to 300.

The clinical course of this type varied considerably. In the mild cases the pain was only slight, the jaundice cleared up in ten to fourteen days and there were very few other symptoms; the temperature was often normal. In the severe cases the temperature would sometimes rise to 103° F., and there would be considerable pain. This type would often last three to four weeks.

Nonjaundiced Cases.—With the exception of jaundice, this group of 36 patients presented essentially the same symptoms as the group of jaundiced patients. The onset here too was sudden with abdominal pain, vertigo, frontal headache, and nausea and vomiting. The temperature was low grade. These patients, though not definitely jaundiced, presented a peculiar characteristic color which gave them a pseudojaundiced appearance. At a distance one would gather the impression that the patient was jaundiced, but upon closer examination it could be seen that there was no actual jaundice and that the scleras were white. The van den Bergh test was negative and the icterus index normal. This type of the disease was more prevalent in patients between the ages of 12 and 16 years than in the younger group.

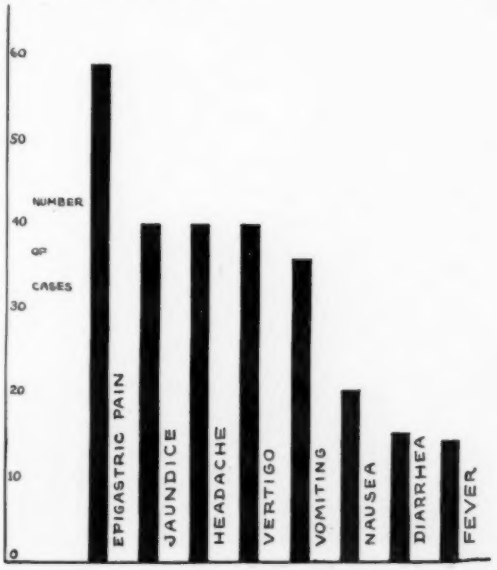

Fig. 2.—Chart showing frequency with which different symptoms were encountered.

CASE REPORTS

CASE 1.—Usual case with jaundice.

T. L., white male, aged 6 years, was admitted to the hospital Nov. 1, 1937, complaining of vomiting, diarrhea, and epigastric pain. The onset occurred on October 29, when he developed nausea; there was no pain or vomiting at that time. On October 30 he vomited and had some epigastric pain. On the next day he developed a severe diarrhea and vomited considerably. On November 1 he had diarrhea, definite jaundice, and the urine was unusually dark. Examination showed an intense jaundice. There was no abdominal tenderness.

The urine was positive for bile. The blood count was as follows: red blood cells, 4,110,000, white blood cells, 7,600, hemoglobin 80 per cent, 53 per cent neutrophiles, 42 per cent lymphocytes, 4 per cent large lymphocytes, and 1 per cent monocytes,

Throat culture contained many short-chained streptococci and staphylococci. The fragility test was normal. On November 2 the van den Bergh was positive direct immediate and equal to 2.5 mg. quantitatively.

During the patient's stay in the hospital he had practically a normal temperature, pulse, and respiratory rate. Two days after admission to the hospital, the abdominal pain disappeared. On November 6 the van den Bergh was positive delayed direct and equal to 1.5 mg. quantitatively. By November 15 the jaundice had practically disappeared.

CASE 2.—A severe case.

P. K., white female, aged 11 years, was admitted to the hospital on Oct. 27, 1937, complaining of pain in the epigastrium, headache, and backache. The onset occurred on October 24 when she developed headache and pain in her eyes. On

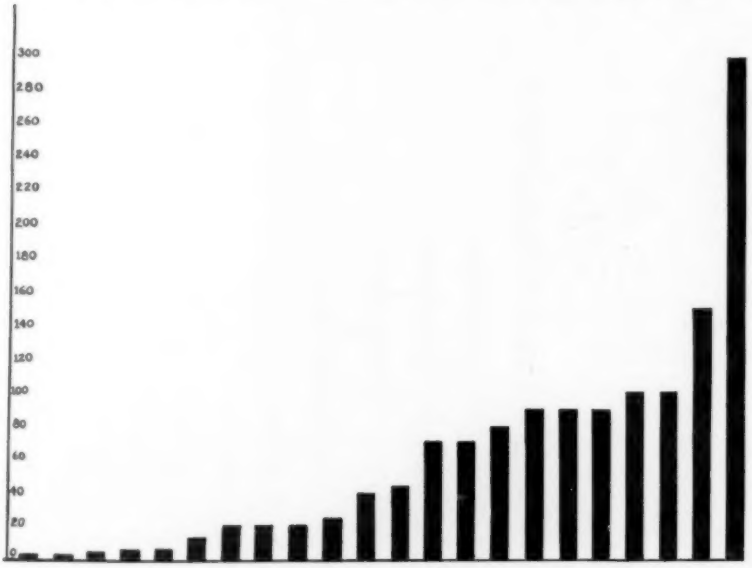

Fig. 3.—Icterus index. Each column represents one case.

October 25 she had backache and anorexia. She was admitted to the hospital on October 27. Examination revealed a well-developed fairly well-nourished white girl 11 years old. The skin and mucous membranes were rather pale, but no jaundice was noted; there was marked tenderness in the epigastrium. Her temperature on admission was 99.8° F.

On October 28 her temperature rose to 102.2° F. There was as yet no jaundice. On October 29 the abdominal pain disappeared, and on the same day she developed marked jaundice. The jaundice increased and reached its height by November 2, thereafter gradually decreasing until November 16, when she was discharged from the hospital. At this time she had no jaundice. The temperature was intermittent from October 27 to Nov. 8, 1937.

The red blood count on admission was 4,180,000; white blood count, 6,450; and hemoglobin content, 81 per cent. The differential count was neutrophiles 52 per cent; small lymphocytes 36 per cent; large lymphocytes 8 per cent; monocytes 3 per

cent; and basophiles 1 per cent. The sedimentation rate was 8 mm. in sixty minutes. The fragility test was normal. Icterus index and van den Bergh were as follows:

DATE	ICTERUS INDEX	VAN DEN BERGH
October 30	100	4 mg. positive immediate direct
November 6	70	1.2 mg. positive delayed direct
November 16	12	0.4 mg. negative direct

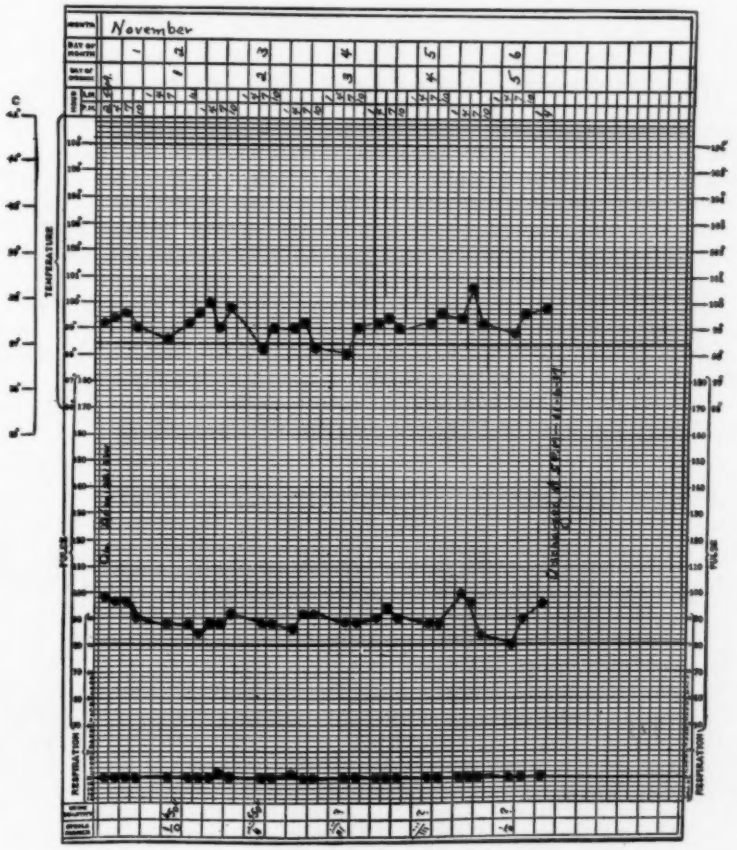

Fig. 4.—Clinical chart of average case.

CASE 3.—A mild case.

P. H., white female, aged 5 years, was admitted Oct. 18, 1937, complaining of jaundice. One week before admission she developed a feeling of malaise and anorexia. Two days before admission she became jaundiced. Physical examination showed definite jaundice and slight enlargement of the liver. The temperature was 100° F. The leucocyte count was 8,200. The differential count was 60 per cent neutrophiles, 30 per cent small lymphocytes, 8 per cent large lymphocytes, and 2 per cent eosino-

philes. The urine contained bile. The fragility test was normal. The icterus index was 20 and van den Bergh was positive immediate direct and equaled 2 mg. quantitatively.

The jaundice gradually decreased. The patient was discharged from the hospital on October 24 and followed in the out-patient department. At the end of two weeks the jaundice cleared up.

CASE 4.—A case without jaundice.

I. K., white male, aged 12 years, was admitted to the hospital Nov. 4, 1937, with the complaints of diarrhea and pain in the epigastrium. A sister of the patient had had these same complaints associated with jaundice three weeks previously. On the day before admission the patient suddenly developed anorexia, diarrhea, slight frontal headache, epigastric pain and nausea, but no vomiting. On the day of admission he had these same symptoms. Physical examination revealed a pseudojaundiced appearance but no definite jaundice. The urine was negative for bile. Throat culture was negative. The red blood count was 4,340,000; white blood count, 6,800; and hemoglobin, 81 per cent. The differential count was normal with neutrophiles 71 per cent, small lymphocytes 20 per cent, large lymphocytes 1 per cent, and monocytes 8 per cent. The blood sedimentation was 11 mm. in sixty minutes. The icterus index was 2 and the van den Bergh was negative direct and equaled 0.1 mg. quantitatively.

The course in the hospital was mild. No real jaundice ever appeared, and the pain disappeared within a day. The temperature on admission was 100° F. rising to 100.4° F. in a few hours but gradually decreasing to normal in a few days. He was discharged Nov. 7, 1937, cured.

DIFFERENTIAL DIAGNOSIS

This disease must be differentiated from the following conditions:

1. Acute appendicitis. The differential diagnosis between these two conditions was often quite difficult in the nonjaundiced cases. The pain and tenderness in the right lower abdomen often simulated that of acute appendicitis. Probably the most important differential point was the facies of these patients—the pseudojaundice was characteristic.
2. Acute gastroenteritis.
3. Influenza. The onset with headache, vertigo, and abdominal pain with moderate fever would frequently simulate that of influenza.
4. Pyelitis.
5. Mesenteric lymphadenitis.
6. Cholecystitis.
7. Acute pharyngitis with referred abdominal pain.
8. Typhoid fever.

COMPLICATIONS

There were practically no complications. The disease usually cleared up in two to four weeks. In one instance there was a recurrence one month after the patient had recovered from the initial attack. Another patient developed an intense jaundice with enlargement of the liver that has persisted for seven weeks. There were no other complications.

TREATMENT

Treatment consisted of (1) rest in bed, (2) fat-free diet, (3) plenty of fluids, (4) sodium phosphate, and (5) sodium citrate.

As a rule the abdominal pain would disappear a few hours after the patient was put to bed. In a number of instances we felt that the disease was aborted by early treatment.

COMMENT

The disease which we have described is apparently an infection which involves the upper intestinal tract and in many instances causes obstruction of the ampulla of Vater with resulting jaundice. The symptoms in those patients who were jaundiced conformed with the usual picture of catarrhal jaundice. However, the possibility of Weil's disease must be considered. Although the classical picture of Weil's disease is that of a much more severe infection, there have been reports of much milder forms of it. Several specimens of convalescent blood from both the jaundiced and the nonjaundiced cases of our group were submitted to the National Institute of Health for agglutination reactions against the *Leptospira icterohemorrhagiae*. The reactions were positive. However, until the present time we have not been able to demonstrate any leptospira in the blood or urine of these patients. It is quite possible that we are dealing with a mild form of Weil's disease. Further studies are now being made on the etiology of this disease and will be reported upon at a later time.

One of the outstanding features of these cases was the persistent vomiting. Although vomiting was not as common a symptom as abdominal pain, it was extremely distressing when it occurred. Sometimes it would persist for two or three days. The jaundice did not cause many secondary symptoms. Most of the patients, in general, were not very sick.

SUMMARY

1. An epidemic of acute duodenitis with and without jaundice occurred during the fall and winter months of 1937-38.

2. The outstanding symptoms were abdominal pain, vomiting, headache, vertigo, and jaundice.

3. Forty cases eventually developed jaundice.

4. Thirty-six cases did not show definite jaundice.

5. The disease was self-limited, usually lasting two to four weeks.

WINDBER HOSPITAL

CONGENITAL SYPHILIS

A Ten-Year Study of Forty-Five Children

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THE following report of 45 children with congenital syphilis under treatment at regular intervals over a period of ten years shows (1) that the infection is amenable to treatment, as the results were satisfactory in 85 per cent; (2) that glucose given in 10 per cent solution to the infected newborn infant in the first four months of life, preceding intravenous neoarsphenamine, is a valuable liver protection; (3) that in several permanent cures, as well as in Wassermann-fast latent congenital syphilitics, adequate treatment for 100 weeks is a satisfactory amount, which need not be exceeded except for special indications; and (4) that central nervous system complication is very damaging and occurs in a high percentage. The general intelligence level of this type of child is demonstrated, and it is shown that only slight improvement in intelligence is to be expected from a long and thorough course of treatment.

Findlay,[1] in 1924, stated in "Reflections on Congenital Syphilis" that "the curative type of treatment is a failure." Thus in his opinion the only way to cure an infant was to start in the antenatal period. With our present better understanding of adequate treatment, and our knowledge that active persistent treatment must be carried on for eighteen months, we know congenital syphilis can be cured. We realize, even more than before, the wisdom of prenatal treatment, but in spite of its general application in the past few years, 60,000 syphilitic infants are born yearly[2] and require care.

Forty-five children with congenital syphilis were followed from two to ten years in the period Jan. 1, 1928, to Jan. 1, 1938. The average length of follow-up was 5.6 years; eleven children, or one-quarter of the group, were followed seven years or more. Central nervous system infection evidenced by positive spinal fluid findings was present in eleven, or 24 per cent. The presence of keratitis was noted in eight children, or 17 per cent. Eighth-nerve deafness appeared in three. Hutchinson's teeth appeared in seven instances. The intelligence quotients were determined in twelve children. The optimal amount of treatment for this type of patient has been uncertain. The children who came under treatment during the first year responded well in five instances out of the six, or 87 per cent, while those who appeared at an age older than 3 years did not respond nearly so well. Children whose

From the Children's Department, Henry Ford Hospital.

serum became negative became so after an average of forty-nine weeks of treatment, while those whose infection became latent and who still have positive Wassermann tests, had an average of seventy-three weeks of treatment. One child in this series died of pulmonary tuberculosis, and six with nervous system infection, are in unsatisfactory clinical condition. Thus 85 per cent of these children are in a satisfactory clinical condition. An outstanding observation is the varied response to treatment: some children have a natural ability to overcome this infection with surprisingly little help, and others fail to progress satisfactorily in spite of heavy medication. It is for this latter group that limits of necessary therapy are sought.

SPECIAL METHOD OF TREATMENT DURING EARLY MONTHS OF LIFE

Six of the forty-five patients came under treatment before they were 6 months old—three of these at birth. The very early cases presented a difficult problem because of the heavy infection of the liver, because of the circulating treponemas, and because of the danger of intoxicating the already infected liver. Because of these dangers, immediately preceding the injection of the first course of neoarsphenamine, 50 to 100 c.c. of 10 per cent glucose was administered as a protection for the liver cells. The dosage of neoarsphenamine, which varied with the size of the baby, was between 50 and 100 mg. Three case abstracts are given as examples.

CASE 1.—M. H., female, No. 206598.

History.—Mother had a positive Wassermann test. The child was normal at birth but did not gain weight. She entered the hospital at 6 months of age, weighing 12½ pounds.

Examination.—The patient was small and poorly nourished. The liver and the spleen were large; lymphadenopathy was general. The blood and the spinal fluid were strongly positive.

Course.—From October 18 to November 28, 50 c.c. of 10 per cent glucose and 60 mg. neoarsphenamine were given intravenously six times at weekly intervals. In the next two years there were fifty-six weeks of treatment with neoarsphenamine and heavy metal. The spinal fluid was completely negative for three years. The blood was negative for one year.

CASE 2.—R. A., male, No. 194086.

History.—The mother's Wassermann reaction was positive. No treatment was given during pregnancy.

Examination.—Patient was admitted at 4 months of age with lobar pneumonia, macular rash, enlarged spleen, and positive Wassermann reaction on the blood and the spinal fluid.

Course.—From December 7 to January 13 six treatments of 100 mg. neoarsphenamine were given preceded by 100 c.c. of 10 per cent glucose. During the first year twenty weeks of treatment with neoarsphenamine and mercury were given. Wassermann reactions have been negative on blood and spinal fluid for four years; child is well, and there is no sign of infection.

CASE 3.—T. R., female, No. 196054.

History.—The mother had syphilis, was treated two weeks during pregnancy, and was Wassermann-positive at term.

TABLE I

RESULTS IN YOUNG INFANTS: NEOARSPHENAMINE PRECEDED BY GLUCOSE IN FIRST COURSE

NO.	NAME	SEX	AGE AT START OF TREATMENT (MO.)	TOTAL WEEKS OF TREATMENT	TOTAL YEARS OF OBSERVATION	INITIAL WASSERMANN		TYPE AND AMOUNT OF TREATMENT								COMMENT
								NEOARS.		SULPHARS.		BISMUTH†		MERCURY		
						BLOOD	S. F.	NO. INJ.	GM.	NO. INJ.	GM.	NO. INJ.	GM.	NO. INJ.	RUBS	
1	R. A.	M	4	20	4	+	+	9	1.0	1	0.1				31	Cure*
2	J. D.	F	1	53	3	+	+	9	0.550	7	1.4	1	0.022		145	Unsatisfactory
3	M. H.	F	6	56	4	+	+	24	3.7			32	0.704			Cure
4	A. L.	M	3	33	6	+	0	8	4.0	4		14				Cure
5	B. P.	F	1	96	6	+	0	32	1.6	12	2.7	24	0.538	38		Cure
6	T. R.	F	1	22	2	+	0	3	0.15	2	0.150			5	63	Cure
Average			2.6	46	4.1											

*Cure, normal blood and spinal fluid. No remaining signs.
†Available metallic bismuth.

Examination.—Birth weight was 6 pounds 11 ounces. The spleen was large, and cord blood was positive.

Course.—The patient was given sulpharsphenamine twice, 50 mg. once and 10 mg. once intramuscularly, and three mercury rubs in the first five days of life. She was admitted then with generalized rash. Six weeks' feeding was given without treatment, and then three neoarsphenamine injections preceded by glucose, 50 c.c., 10 per cent. During first year, twenty-two weeks of treatment with neoarsphenamine and mercury were given. The Wassermann test has been negative for three years, and no signs are present.

The six patients received from twenty to ninety-six weeks of treatment, and all but one, whose cooperation was poor, were cured in an average of forty-five weekly treatments. The giving of glucose as a protection before arsenicals intravenously in the newborn infant was especially beneficial to T. R. (Case 3) who was sensitive to arsenic as shown clearly by a rash after sulpharsphenamine. The total of treatment was divided between arsenicals and heavy metals about equally, as shown by Table I.

The fetal circulation differs in a few very characteristic ways from the postnatal circulation. One of the differences is the way in which a large part of the freshly oxygenated, or placental, blood, coming by way of the umbilical vein, circulates through the liver before it continues through the ductus venosus to the inferior vena cava and thence through the entire fetal circulation. In this manner all constituents or infectious matter in the blood from the placenta bathe the liver cells thoroughly first before passing through the rest of the fetal organs. The spirochetes of syphilis are known to invade the placenta in early types of the disease, thence to invade the fetal blood stream, and then to spread by means of it. Thus the organisms have an opportunity to come in close contact with liver tissue, and many investigators have shown that the spirochetes tend to invade and intoxicate this tissue. Griffith and Mitchell[3] state that changes in the liver in syphilis of the newborn are nearly always present. The organ is enlarged, firm, hard, irregular; it has a thickened capsule, often miliary nodules, consisting of minute gummas, and an increase of interstitial tissue with atrophy of many hepatic cells. The commonest clinical manifestation is marked enlargement of the liver. Von Reuss[4] states that in syphilis of the newborn 31 per cent have involvement of the liver. Litchfield,[5] in a detailed report of the histology of liver damage in this condition, describes multinucleated masses of new liver cells, capillary distention, and diffuse fibrosis. Stokes[6] states that the treatment of hepatic syphilis is complex and patients must be under careful control. Jeans and Cooke[7] state that 22 per cent of the syphilitic infants die in the first year and that the liver is the organ of choice for demonstration of organisms. Sylvester[8] found a mortality rate of 21.5 per cent from 1920 to 1925;

Holt and McIntosh[9] consider the liver the most frequently attacked organ in the body and warn against acute yellow atrophy under treatment with arsenicals.

This type of overwhelming infection in the newborn period presents a special problem because the drugs used most successfully, the arsenical preparations, have a tendency to irritate the liver. In the patients with an already damaged liver, with many of its cells in a state of atrophy, the protection of this organ becomes the uppermost concern. Its protection during poisoning has been studied experimentally, and many observations are on record. The research of Davis and Whipple[10] established the fact that high carbohydrate diets were for dogs most protective against central necrosis of the liver due to chloroform poisoning.

Craven[11] in study of the same problem but using arsenic as a poison instead of chloroform finds that an 85 per cent protein diet protects better but that liver damage is not common in healthy dogs subjected to arsenic. The question of a protective diet has also been studied by others—Wells,[12] Hunt,[13] Opie and Alford,[14] Graham,[15] Simonds[16] and Hooper, Kolls and Wright,[17] who agree with Whipple that a high carbohydrate diet protects the liver from central necrosis better than high protein diets. Bailey and MacKay[18] in a clinical article state their views strongly that a "diet rich in carbohydrate, low in fat and protein should precede, accompany, and succeed arsenical treatment" in all patients with syphilis. V. Genner[19] in his extensive monograph, "By-Effects in Salvarsan Treatment and Their Prevention," has summarized the literature, and presented the evidence that glucose does actually protect the liver cells, exerts a neutralizing effect on salvarsan as a parenchymatous poison, and involves no additional strain on organs of storing and eliminating arsenobenzols. The preponderance of opinion is that carbohydrate is very necessary as a protective agent in the body during necessary subjection to treatment which may injure the liver. Mortality in syphilis of the newborn and very young infant has been so high that in view of our experience we believe intravenous glucose should be given before neoarsphenamine in the first course of treatment given these patients.

CHILDREN COMPLETELY CURED

Twenty children, or 45 per cent of the group, were completely cured. Three of these had central nervous system infection. The average time of treatment was 48 weeks. The average time for the three with central nervous system infection was 44 weeks. This figure is low because the average was lowered by one child whose treatment was begun at 4 months and who responded in 20 weeks of treatment. The actual number of weeks of treatment varied from 20 to 103. The oldest child to come under treatment and achieve a negative Wassermann reaction did so at the age of 15 years and responded in 60 weeks of treatment carried on over a period of 3 years. The child who had 103 weeks of treat-

ment was a relapser, and her Wassermann reaction changed back and forth. This group received an inadequate amount of treatment according to our present standards requiring 50 continuous treatments in the first year, and, if the Wassermann test be positive on blood or spinal fluid, the same amount the second year. Yet for these children it was enough, and it emphasizes again the variation of response. Details are shown in Table II.

CASES OF LATENT SYPHILIS

Eighteen patients, or 40 per cent of the group of 45, had, at the end of the ten-year period of observation, positive Wassermann tests as the only signs of infection present. These patients are in school or in homes carrying on a regular daily routine and indistinguishable from normal children with two exceptions—one child with eighth nerve deafness and a boy with healed scars of the cornea from a keratitis. These 18 children have been followed intimately for from two to ten years, the average time being 5.2 years, and although the Wassermann test of the blood did not reverse, their high quality of resistance to general infection and ability to meet the requirements of school have seemed a convincing demonstration that syphilis has done them very little harm. The average period of treatment was 73 weeks, and the actual number varied from 41 to 119. Two of the girls in this group have married and have normal children. The two patients with central nervous system infection have developed negative spinal fluids and have done as well as the rest of the group. The average amount of treatment given this group was substantially larger than that given those who developed serologic reversals; however, this group started treatment at 8.9 years of age, whereas the "reversals" group started treatment at an average of 6 years. It is true, though, that the best results were obtained with the least treatment; this fact emphasizes again the great variation in ability to respond. We have considered as clinically satisfactory all of this latent group. The use of mercury or bismuth preparations over a longer period of time than is really necessary may lead to chronic irritation and weakening of liver and kidney parenchyma. It is important to limit the amount of treatment to what is really necessary to avoid this slight chance of chronic nephritis, chronic or acute liver damage, and weakening of capillary walls with tendency to local hemorrhage. In small children it is very important to avoid local sclerosis of the gluteal muscle and to avoid painful injections which are not necessary. Details of treatment are shown in Table III.

CASES CLINICALLY UNSATISFACTORY

Seven children did not respond well and were clinically in an unsatisfactory condition at the last observation. Six of these were complicated by nervous system infection. Two had tuberculosis, one of whom died.

TABLE II

RESULTS AND AMOUNT OF TREATMENT IN CHILDREN CURED: NEGATIVE BLOOD AND SPINAL FLUID REACTIONS IN ALL PATIENTS

NO.	NAME	SEX	AGE AT START OF TREATMENT (YRS.)	DURATION IN YEARS OF TREATMENT	TOTAL WEEKS OF TREATMENT	TOTAL YEARS OF OBSERVATION	INITIAL WASSERMANN		TYPE AND AMOUNTS OF TREATMENT								COMMENT
									NEOARSPH.		SULPHARSPH.		BISMUTH†		MERCURY		
							BLOOD	S. F.	NO. INJ.	GM.	NO. INJ.	GM.	NO. INJ.	GM.	NO. INJ.	NO. RUBS	
1	R. A.	M.	4/12	1	20*	4	+	+	9	1.0	1	0.1				51	Cured.
2	J. D.	M.	7	2	57	5	+	0	23	7.8			25	0.550		9	Cured.
3	M. F.	F.	15	3	60	4	+	0	14	7.3			30		16		Cured.
4	H. G.	F.	9	2	21	4	+	0	7	3.5			5	0.111	9		Cured.
5	F. G.	M.	14	2	25	3	+	0	6	2.4					5		Cured.
6	M. H.	F.	6/12	2	56	4	+	+	24	3.7			32				Cured.
7	A. L.	M.	3/12	2	33	6	+	0	8	0.4	4		7	0.154	14		Cured.
8	B. L.	F.	11	4	62	4	+	0	18	9.7			18		6	100	Cured.
9	R. M.	F.	8	1	6	6	+	0	4	2.0			2				† Diagnosis.
10	A. M.	F.	4	2	49	6	+	0	6	1.2			8		1		Cured.
11	W. O.	M.	8	8	102	9	+	0	23	8.9			19	0.418	20		Cured.
12	B. P.	F.	1/12	4	96	6	+	0	12	2.7			24	0.528	13		Cured.
13	T. R.	F.	1/12	1	22	2	+	0	3	0.15	2	0.15			5	63	Cured.
14	W. R.	M.	3	2	57	5	+	+	26	15.6			16	0.352	15		Cured.
15	I. R.	F.	4	1	29	7	+	0	17	4.1	2	0.6	8	0.176	4		Cured.
16	M. S.	F.	6	4	60	10	+	0	12	2.4			6		6		Cured.
17	B. T.	M.	12	3	43	10	+	0	12	6.6			8		12		Cured.
18	W. T.	M.	14	3	49	4	+	0	6				8		8		Institution case—feeble-minded. S. F. normal.
19	B. Z.	M.	7	2	46	6	+	0	21	6.7			19	0.418	8		Cured.
20	H. Z.	F.	11	7	103	7	+	0	25	11.25			47		7		Cured.
Average			6.7		49.0	5.7											

*Mercury rubs 5=1 week's treatment.
†Available metallic bismuth.

TABLE III

CHILDREN WITH LATENT SYPHILIS—POSITIVE BLOOD WASSERMANN REACTIONS AT LAST OBSERVATION AND NO SIGNS OF ACTIVITY (40 PER CENT OF GROUP)

NO.	NAME	SEX	AGE AT START OF TREATMENT (YRS.)	DURATION IN YEARS OF TREATMENT	TOTAL WEEKS OF TREATMENT	TOTAL YEARS OF OBSERVATION	INITIAL WASSERMANN		TYPE AND AMOUNTS OF TREATMENT								COMMENT
									NEOARS.		SULPHARSPH.		BISMUTH*		MERCURY		
							BLOOD	S. F.	NO. INJ.	GM.	NO. INJ.	GM.	NO. INJ.	GM.	NO. INJ.	NO. RUBS	
1	H. D.	M	7	3	77	3	+	0	3	2.2	6	1.2	56	1.232	7		
2	T. D.	F	8	2	41	2	+	0	12	3.6			29	0.638			Still under treatment.
3	M. D.	F	11	6	109	10	+	0	30	12.4			16	0.352	14		Has two normal children.
4	R. D.	F	7	5	120	10	+	0	22	9.0			16	0.352	18		
5	E. H.	M	6	2	44	2	+	0	19	6.3			10	0.220	15		
6	F. H.	M	8	2	40	2	+	0	15	4.5			10	0.220	15		
7	N. H.	F	10	2	60	2	+	0	9	2.3			31			40	Acetarsone 12 weeks.
8	J. L.	F	6	5	113	8	+	+	36	11.25			33	0.726	20	118	
9	V. L.	F	11	3	64	4	+	0	28	15.5			19	0.418	7	50	
10	G. L.	M	13	3	71	10	+	0	29	14.7			30	1.344	12		
11	E. M.	M	9	5	60	5	+		24	9.6			8	0.176	7		
12	A. N.	M	10	5	103	9	+	0	19	10.4			16		21		
13	M. O.	F	12	3	69	5	+	0	24	9.7			24	0.528	16	25	
14	B. Q.	M	8	4	92	5	+	0	34	12.65	4	0.8	45	0.440	9		
15	H. Q.	F	3	5	64	5	+	+	26	7.4	7	1.4	30	0.660	1		
16	V. S.	M	7	4	84	8	+	0	28	11.3	1	0.2	21	0.462	24	60	
17	M. T.	F	14	2	43	2	+	0	10	3.3			1	0.022	8	50	Has one normal child.
18	S. V.	M	11	3	61	3	+	0	23	7.3			38				
Average			8.9		73	5.2											

*Available metallic bismuth.

TABLE IV

UNSATISFACTORY RESULTS—CHILDREN WITH SIGNS OF INFECTION AT LAST OBSERVATION

NO.	NAME	SEX	AGE AT START OF TREATMENT (YRS.)	DURATION IN YEARS OF TREATMENT	TOTAL WEEKS OF TREATMENT	TOTAL YEARS OF OBSERVATION	INITIAL WASSERMANN		TYPE AND AMOUNTS OF TREATMENT								COMMENT
									NEOARS.		SULPHARSPH.		BISMUTH*		MERCURY		
							BLOOD	S. F.	NO. INJ.	GM.	NO. INJ.	GM.	NO. INJ.	GM.	NO. INJ.	NO. RUBS	
1	R. B.	F	9	2	34	9	+	+	12	3.0			8	0.176	14		Institution mental care.
2	J. D.	F	3/12	3	52	3	+	+	10	0.75	7	1.4	1	0.022		140	Acetarsone 6 wks., poor cooperation.
3	E. G.	F	10	3	49	10			6	5.4							Advanced adult T.B.
4	B. H.	F	12	2	61	2	+	0	23	8.2			38	0.584			Fixed pupil as result healed CNS.
5	J. H.	F	4	2	58	2	+	+	7	1.8			31			40	Acetarsone 12 weeks.
6	E. L.	F	11	4	55	4	+	0	21	7.6			17	0.374	17		Dead—pul. T.B.
7	H. W.	F	2	7	120	7	+	+	15	4.5	13	2.84	33	0.726	21		CNS Syph.
Average			6.8		71	6.1											

*Available metallic bismuth.

One child has a fixed pupil as the result of old healed basilar meningitis during which the spinal fluid became negative. Two are inferior mentally, one of whom is under institution care. The treatment averaged 71 weeks, but, if corrected by omitting the patient who died and the two under institution care, the average is 73 weeks of treatment. Details are shown in Table IV.

CHILDREN WITH POSITIVE SPINAL FLUID REACTIONS

An important question is, What extra hazard is associated with nervous system infection? Eleven patients, or 24 per cent of the entire group, had positive spinal fluid findings. Here we had 6, or 54 per cent, unsatisfactory cases, by far the poorest results. However, 3 children had complete reversal, all coming under treatment at the age of 3 years or younger, and 2 developed negative spinal fluid reaction, retaining a latent positive blood. Details of the response of this group are shown in Table V.

INTELLIGENCE QUOTIENT STUDY

Studies have been made of the mentality in 12 patients of the group and show by the modified Binet-Simon scale values mostly subnormal. Studies were repeated in from 1 to 4 years to obtain an estimate of the rise of mentality with treatment or the instability of mental processes in the course of the disease. Eight of the patients were in the dull group with I. Q.'s of 80-90, while only 4 reached the lowest limits of normal. Seven have improved and 5 remained the same under treatment. Observations extend over 4 years in 7 patients. Nine of them are sociable, likable children, and all are able to do housework or a simple trade. Details are shown in Table VI.

COMMENT

Smith[20] reports that 86.9 per cent of his group of congenital syphilitics had ultimately a clinical outcome which was satisfactory, which may be compared with 85 per cent in this group. His 10.2 per cent incidence of central nervous system involvement was somewhat lower than the 24 per cent which appeared here. His observation that more than 50 weeks of treatment should be given to the patient with latent syphilis to prevent relapse or progression agrees with my experience. Adequate treatment is well summarized by Cole[21] and must be given by one-year and six-month periods with emphasis on final result rather than on reversal of the Wassermann test. Moore[22] has stated clearly that the child with late congenital syphilis and Wassermann fastness should have continuous treatment for two years and then, in absence of signs of activity, should be placed on probation. The present series bears this statement out, and my opinion is that there must be definite indications to justify carrying on treatment for more than two years. The intelligence

TABLE V

CASES WITH CENTRAL NERVOUS SYSTEM INFECTION

NO.	NAME	SEX	AGE AT START OF TREATMENT (YRS.)	TOTAL WEEKS OF TREATMENT	TOTAL YEARS OF OBSERVATION	WASSERMANN TEST				COMMENT
						BLOOD		SPINAL FLUID		
						INITIAL	LAST	INITIAL	LAST	
1	R. A.	M	4/12	20	4	+	0	+	0	Home and attending regular school.
2	M. H.	F	6/12	56	3	+	0	+	0	Home and attending regular school.
3	W. R.	M	3	57	4	+	0	+	0	Home and attending regular school.
4	J. L.	F	6	112	6	+	+	+	0	Home and attending regular school.
5	H. Q.	F	3	64	3	+	+	+	0	Home and attending regular school.
6	R. B.	F	9	34	9	+	+	+	+	Institutional care—feeble-minded.
7	J. D.	F	3/12	47	3	+	+	+	+	Home, regular school. No cooperation in receiving treatment.
8	E. G.	F	10	89	9	+	0	+	0	Hospital for tuberculosis—8 years. Poor ability to heal.
9	B. H.	F	12	61	2	+	+	0	0	Home and attending regular school.
10	J. H.	F	4	58	2	+	+	+	+	More treatment necessary to reverse spinal fluid.
11	H. W.	F	2	120	6	+	0	+	0	Mental problem—feebleminded.
Average			4.5	65	4.6					

TABLE VI

PROGRESS OF INTELLIGENCE QUOTIENT IN CONGENITALLY SYPHILITIC CHILDREN UNDER TREATMENT

NO.	NAME	SEX	BLOOD WASSERMANN		SPINAL FLUID WASSERMANN		INTELLIGENCE QUOTIENTS UNDER TREATMENT				COMMENT
			EARLY	LATE	EARLY	LATE	1ST YEAR	2ND YEAR	3RD YEAR	4TH YEAR	
1	H. D.	M	+	+	0	0	82			92	Home and regular school.
2	T. D.	F	+	+	0	0	80	73			Home and regular school.
3	B. H.	F	+	+	0	0	87	90			Home and regular school.
4	J. H.	F	+	+	+	+	85	85			Home and regular school.
5	N. H.	F	+	+	0	0	79	80			Home and regular school.
6	E. L.	F	+	+	0	0	75		82		Dead—pulmonary tuberculosis
7	J. L.	F	+	+	+	0	95			93	Home and regular school.
8	B. Q.	M	+	+	0	0	78			87	Home and regular school.
9	H. Q.	F	+	+	+	0	84			93	Home and regular school.
10	S. V.	M	+	+	0	0	77			83	Home and regular school.
11	H. W.	F	+	0	+	0	85			90	Home and regular school.
12	H. Z.	F	+	0	0	0	66			73	Home and regular school.

level was low in this group, and the factors affecting it, i.e., inheritance, disease, nutrition, cannot be separated. We can say, however, that treatment and a high standard of nutrition changed the level of intelligence very little.

We believe a child has the best chance of recovery when placed under treatment as early as possible, preferably before 4 months of age. A central nervous system infection will respond better than ever again if treatment is started at this early age, before nerve tissue has been intoxicated and destroyed. The major complications of interstitial keratitis and deafness can be prevented. An adequate amount of treatment means 48 weekly injections during the first year, 24 of them of an arsenical, and 24 of a heavy metal in three alternating courses of 8 injections of each. The most satisfactory amount of neoarsphenamine to use has been 0.01 gm. per kilogram of body weight per week, but in no cases have we given more than 0.600 gm. per injection in childhood. We have discontinued the use of mercury because bismuth has proved more effective. Ample dosage of bismuth is approximately 0.5 mg. per kilogram per day, and our dosage is now approximately 1 mg. per pound of weight per week. The water-soluble bismuth sodium tartrate has 11 mg. available metallic bismuth per cubic centimeter and is a satisfactory and nonirritating preparation to use in the infants and smaller children. The oil-soluble bismuth camphenilanate (cyclobis) contains 30 mg. available metallic bismuth per cubic centimeter and is a satisfactory preparation for the older and larger children. Here again we have not given higher than a maximum dose of 60 mg. metallic bismuth per week regardless of weight. If the Wassermann test is positive on either spinal fluid or blood at the end of the first year, a second year of the same type of treatment is recommended. If, however, both blood and spinal fluid are negative after one year of treatment, a further six-month course of treatment is recommended, consisting of 8 injections of arsenical, and 16 injections of bismuth. The patient is then placed on probation, and the Wassermann test is checked at first every six months and later once yearly for five years. If the patient, however, has a positive spinal fluid infection, special treatment must be carried into the third year; in many cases it may be necessary to continue treatment for several years, as these are the cases which give the poorest results. Hyperthermia by the Kettering hypertherm is our method of choice, but malarial infection is used freely also.

SUMMARY

A group of 45 congenital syphilitic children were studied for ten years with an 85 per cent final clinically satisfactory result.

Infants in the neonatal period or early infancy should have the first course of neoarsphenamine preceded by 10 per cent glucose intravenously as protection to the liver and to counteract the well-known toxic effects common in this period.

Complete serologic and clinical cure was observed in 45 per cent, or 20 children, with an average of 49 weeks of treatment.

Latent syphilis with an irreversible Wassermann reaction was observed in 40 per cent, or 18 children, but these were practically as well as the former group. A positive Wassermann test on the blood in the absence of other clinical signs after two years' adequate care is not indication for further treatment.

Central nervous system infection, the most serious complication, occurred in 24 per cent of this group, gave 54 per cent unsatisfactory result, and calls for early and persistent treatment.

Mentality of these children was below average and treatment had a slightly beneficial effect, as judged by the estimation of the intelligence quotients, but 7 of 12 cases remained below normal. Environmental and heredity factors cannot be separated from the disease factor.

Studies of the intelligence quotients of these children were done by Dr. E. L. Schott, of the Neuropsychiatric Department.

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MOLD SPORE CONTENT OF THE AIR IN BOSTON

With Reference to Atopic Sensitivity

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DURING the past two years the literature has contained several reports[1-11] on the production of vasomotor rhinitis and asthma by air-borne mold spores acting as atopic excitants. Up to 1936 cases of this nature were considered relatively rare and the literature contained only scattered case reports and incomplete mold surveys.[12-25] In this year Feinberg[1-4] first demonstrated the prevalence of these molds in the air around Chicago and reported a series of 68 cases, later expanded to 90, showing atopic sensitivity to these molds. Treatment was carried out in 60 cases with excellent results. Most of these patients, however, also received pollen therapy.

Both Feinberg's report and a more recent communication by Durham[10] demonstrated a seasonal fluctuation of air-borne molds. Durham confined his study to Alternaria. He showed that the atmospheric contamination by this mold as evidenced by the gravity method is quantitatively in the neighborhood of ragweed. This is particularly true in the wheat belt. Lamson and Rogers,[7] Brown,[6] and Vander Veer[9] have shown the prevalence of positive skin tests to mold spore extracts.

The purpose of the present paper is to report on the daily mold contamination of the air around Boston, the incidence of respiratory, atopic sensitivity to these molds among children, the reaginic content of their sera, and the effectiveness of specific treatment in asthma and hay fever.

METHOD

Daily Mold Counts.—Sterile Petri dishes measuring 9 cm. in diameter, the bottoms of which had been covered with a thin layer (1.5 to 2 mm.) of sterile, solid Sabouraud's medium, were exposed daily to the outside air for a half hour on a first floor window sill, four feet above which there was a wooden platform. The exposures were made at approximately the same time each morning. The general location was a large courtyard containing trees, in the more thickly populated suburbs of Boston. Plates exposed for a few days in a more thinly populated suburban area surrounded by oak woods and on a third floor window sill of a denser area showed little variation in quantity or types of molds from those found at the main station. It was therefore assumed that the daily counts were fairly representative of the surrounding country.

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A thin layer of Sabouraud's medium was chosen instead of the potato medium recommended by Feinberg[26] because on this medium, when poured thinly, the mold colonies were smaller, preventing mutual overgrowth, and thereby facilitating identification. The Petri dishes were incubated at room temperature for four to seven days. The colonies were then identified both by gross and microscopic examination. No effort was made to classify the molds beyond genus. The summary of Gilman and Abbott[27] and Henrici's book[28] were used for aid in identification.

Preparation of Extracts.—During the earlier part of the investigation, commercial extracts were used. As the prevalence of mold sensitivity became apparent, the extracts were made in our own laboratory. After trying several methods of preparation, the following was used because of its simplicity and ability to produce relatively powerful extracts: The mold to be extracted was first isolated in pure culture and then inoculated into 250 c.c. flasks containing 40-50 c.c. of liquid Sabouraud's medium. After twenty to forty days the flasks were opened, and the powdery surface of the mat was moistened with a few drops of ether so as to facilitate the mixing of the dry spores with the liquid medium. The entire content of the flask was then poured into a sterile mortar, and the mat was ground thoroughly in the medium. This was allowed to stand for twenty-four hours in the icebox and was then filtered through paper followed by Seitz filtration. Such extracts contained on the average about 4 mg. of nitrogen per cubic centimeter after subtracting the amount of nitrogen in the medium itself. However, since a large part of this nitrogen undoubtedly is derived from the mycelian threads instead of the spores and since the sensitizing properties of the mycelia are open to question, no effort was made to standardize the extracts on a nitrogen basis.

Testing.—All skin tests were done intracutaneously, with approximately 0.01 c.c. of the undiluted extracts for each test. In view of the fact that the subjects were all children, this procedure was deemed safe because of the comparative rarity of constitutional reactions in the younger age groups. Results were read in ten to fifteen minutes and recorded graphically with measurements in millimeters of the maximum diameter of the wheal and flare. Control sites consisted of Sabouraud's medium in many instances. However, this was found to be completely inactive as would be expected from its lack of protein content.

Passive Transfers.—These were done in the usual manner. Sites, of 0.1 c.c. each, of the patient's serum were prepared intracutaneously on the recipient's arm. Twenty-four to forty-eight hours later the prepared sites and control sites were tested with approximately 0.01 c.c. of the extracts.

Treatment.—This was carried out in the same manner as pollen therapy by the subcutaneous injection of dilutions of the extracts of

the mold which was at fault, usually Alternaria. The initial dose was usually 0.1 c.c. of the 1/1000 dilution, although occasionally higher dilutions were required in cases of extreme sensitivity. An occasional mild systemic reaction was encountered.

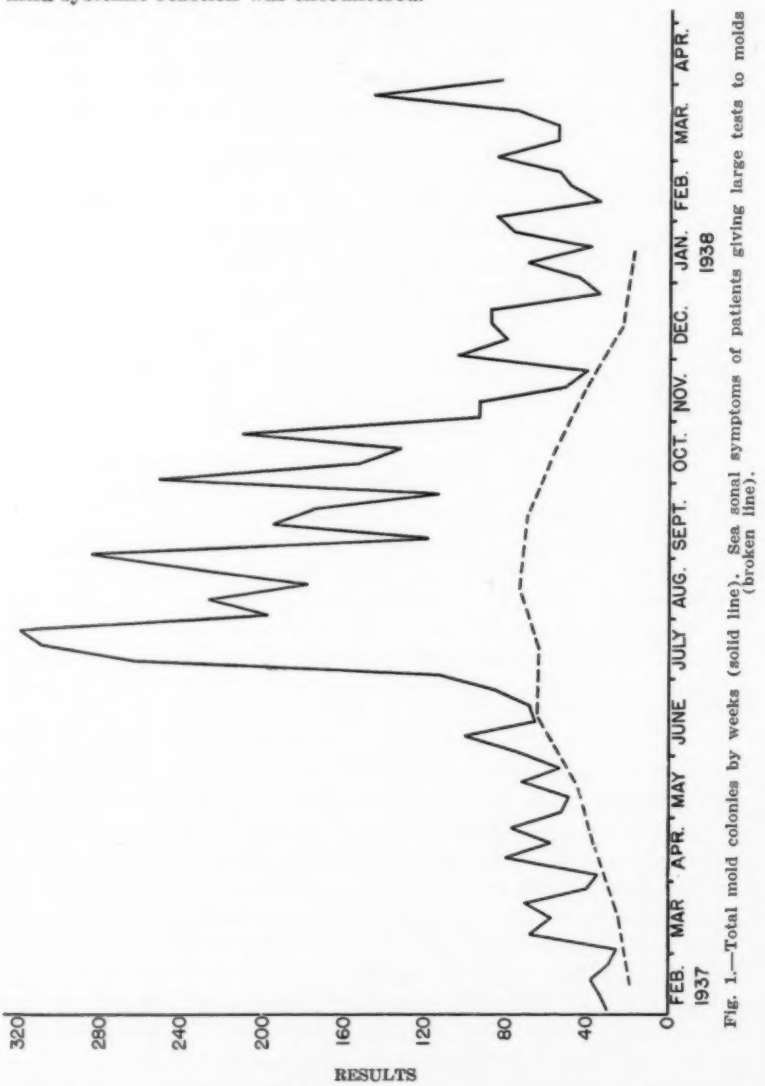

Fig. 1.—Total mold colonies by weeks (solid line). Seasonal symptoms of patients giving large tests to molds (broken line).

1. *Mold Contamination of the Air.*—Only a relatively few genera of molds appeared with any regularity on the daily exposed Petri dishes. These were Alternaria, Hormodendrum, Chaetomium, Aspergillus, Penicillium, and many colonies which could not be identified because of

their failure to produce spores. This latter group will be referred to as nonsporebearers. Fig. 1 shows the total number of colonies by weeks from Feb. 3, 1937, to April 13, 1938. It will be noted that from early

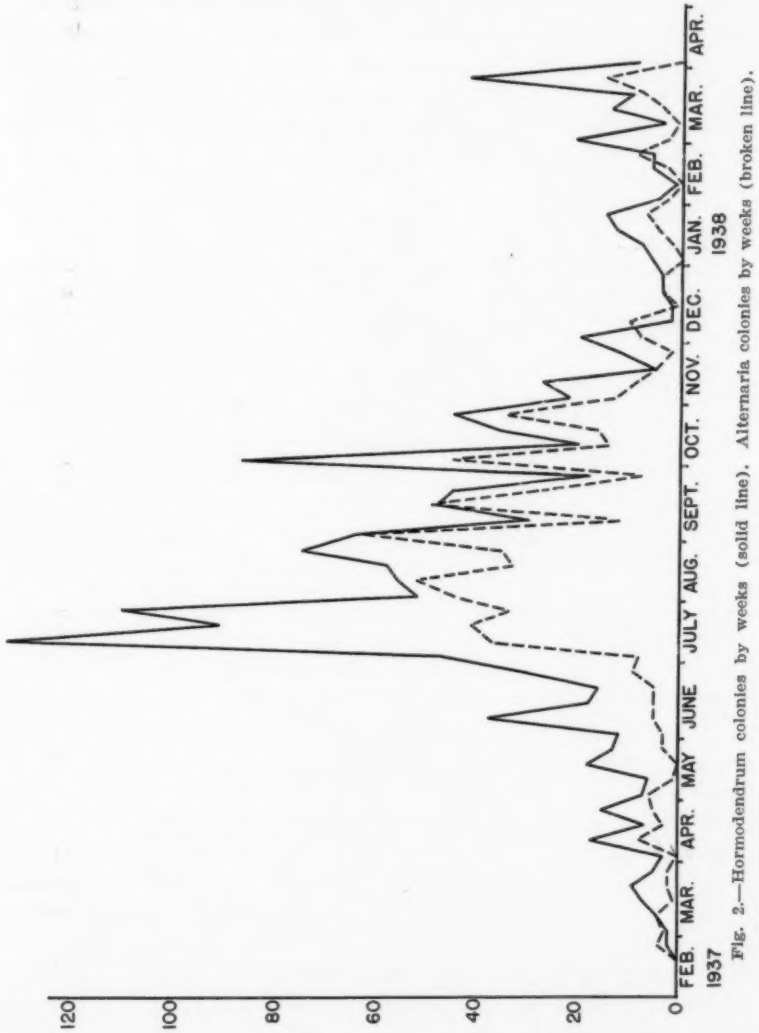

Fig. 2.—Hormodendrum colonies by weeks (solid line). Alternaria colonies by weeks (broken line).

July to mid-November there is a markedly increased mold content of the air. Alternaria, Hormodendrum, and nonsporebearers are almost entirely responsible for this increase. Reference to Fig. 2 will show how closely the curves for Alternaria and Hormodendrum match the total mold curve. Aspergillus, Penicillium, and Chaetomium fail to show

any seasonal incidence. They appear uniformly throughout the year in small quantities with the possible exception of Chaetomium which seems to display a slight increase from the middle of August through September. Further observations will have to be made on this mold.

The daily fluctuation in the number of colonies on the plates was very marked. This was also true of plates exposed every four hours for forty-eight hours. An effort was made to correlate this fact with temperature, relative humidity, wind direction and velocity, sky, and precipitation. The only conclusion which could be drawn was that over a period of several days of hot, moderately clear weather following several days of moist weather resulted in an increase of colonies. Hourly fluctuations in weather conditions showed no correlation with the number of colonies.

2. *Clinical and Skin Sensitivity.*—The patients studied were all atopic children, ranging in age from 1 to 12 years. The seasonal incidence of rhinorrhea or asthma in all children who gave convincing skin reac-

TABLE I

INTRACUTANEOUS TESTS ON 177 UNSELECTED CHILDREN SUFFERING FROM RESPIRATORY ALLERGY

	0 0	± ±	6 20 +	10 25 ++	15 35 +++	20 45 ++++	% showing +++ or ++++ reactions
Alternaria	75	18	24	16	23	21	25
Aspergillus	100	22	15	19	6	0	4
Hormodendrum	95	28	14	10	8	3	6
Penicillium	107	21	14	6	4	0	2.5

tions to molds is represented by the dotted line in Fig. 1. It will be noted that the symptoms are greatest during the periods of greatest contamination of the air by molds. There are also slight exacerbations of symptoms during the grass and ragweed pollenating seasons. This is due to the frequent coexistence of pollen and mold sensitivity in the same patient. In previous years several of these patients were thought to be pure pollen cases, but when their records were carefully scrutinized, it was observed that they continued their symptoms in a milder form during late July and early August when the air is relatively free of pollen around Boston. Their symptoms also continued into the late autumn several weeks after the ragweed pollen was entirely out of the air. The results of specific treatment in these patients were greatly improved by including mold, usually Alternaria, with their pollen

therapy. Several mold-sensitive patients had mild symptoms throughout the year with exacerbations during the summer and fall months.

Table I gives the results of intracutaneous tests to the four commonest molds in 177 unselected atopic children suffering from respiratory symptoms, mostly asthma. The size of the reactions are indicated at the top of the table, the figures representing the greatest diameter of the wheal and flare in millimeters. Twenty-five per cent of the patients gave +++ or ++++ reactions to Alternaria, whereas Aspergillus, Hormodendrum, and Penicillium elicited large reactions in only 4, 6, and 2.5 per cent of cases respectively. Clearly, from the point of view of skin tests, Alternaria is by far the most important mold.

3. *Demonstration of Reagins.*—An effort was made to demonstrate reagins in the sera of unselected patients giving ++ or greater skin tests, using the usual technique for passive transfer as described above. The results are tabulated in Table II. Reactions are reported as weakly

TABLE II

PASSIVE TRANSFERS IN PATIENTS GIVING ++ OR GREATER REACTIONS TO MOLDS

	TOTAL	NEGATIVE	WEAKLY POSITIVE	STRONGLY POSITIVE	PER CENT POSITIVE
Alternaria	26	2	4	20	92%
Aspergillus	8	6	2	0	25%
Hormodendrum	10	5	1	4	50%
Penicillium	6	3	2	1	50%

positive when the wheal and flare at the prepared site is ++ and definitely larger than at the control site. Strongly positive reactions are +++ and ++++ with negative controls. Reagins to Alternaria were easily demonstrated in 24 of the 26 trials, whereas reagins to Aspergillus, Hormodendrum, and Penicillium were present only about half the time.

4. *Results of Specific Therapy.*—Table III shows the results of specific therapy in 34 patients. Of these, 23 received both pollen and mold treatment. Many of the patients in this group had been treated with pollen only in previous years with poor results. The improvement when

TABLE III

RESULTS OF SPECIFIC THERAPY

Patients treated with pollen and Alternaria		23
Result good (75-100%)	13	
Result fair (25-75%)	6	
Result poor (0-25%)	4	
Patients treated with Alternaria alone		7
Result good	5	
Result fair	0	
Result poor	2	
Patients treated with Alternaria and/or other molds		4
Result good	4	
Result fair	0	
Result poor	0	

Alternaria was included was striking in many instances. More convincing are the results obtained in eleven patients in whom mold treatment alone was administered. Nine received practically complete freedom from symptoms.

DISCUSSION

The results of this investigation confirm the work of Feinberg[1-4] in most details. The similarity between his daily mold counts in Chicago and those presented here for Boston is striking.

Perhaps the most important feature of the present study is the prominent place which Alternaria assumes. Except for Hormodendrum, which has a much smaller spore, and nonsporebearers, Alternaria is the most prevalent mold in Boston; it has a definite seasonal increase in quantity; it reacts strongly on the skin of atopic children most frequently; it is a potent excitant to the formation of reagins; and specific therapy with its extract is very effective in properly selected cases. As Durham[10] has pointed out, the Alternaria spore is much the largest of the common air-borne molds. In view of its prevalence and size, which approaches that of a ragweed granule, it is not surprising that it is an important excitant of atopic sensitivity.

It will be noted that no effort has been made to identify the species of molds appearing on the daily plates or to test or treat with any particular species. Studies in progress at present would indicate that differentiation of the molds beyond the genus is in most instances unnecessary. This is quite analogous to the generally accepted experience that the different species of ragweed are immunologically identical.

SUMMARY

1. Following the method of Feinberg, Petri dishes containing Sabouraud's medium were exposed to the outside air for a half hour each day for fourteen months. Alternaria, Hormodendrum, and nonsporebearing molds were found to increase in quantity gradually during the spring months, to increase rapidly during July, August, and September, and to taper off during October and November. Aspergillus, Penicillium, and other air-borne molds failed to display a seasonal incidence.

2. Twenty-five per cent of 177 children suffering from asthma and hay fever reacted strongly to Alternaria extracts when tested intracutaneously. A much smaller number reacted to other molds.

3. Reagins to Alternaria could easily be demonstrated in the sera of 92 per cent of 26 children chosen at random from among those giving strong skin reactions to Alternaria. Reagins were less frequently present to other molds.

4. The seasonal incidence of symptoms among those patients giving strong skin tests to molds corresponds closely to the seasonal variations of mold spores in the outdoor air when the effect of coexisting pollen sensitivity is taken into account.

5. During 1937, 34 patients were treated with mold extracts. Twenty-three of these also received pollen therapy. Of the 11 receiving only mold treatment, 9 obtained marked relief, and only 2 failed to benefit.

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Critical Review

DISORDERS OF GONAD FUNCTION IN CHILDREN

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THE mass of literature dealing with the physiology of the sex glands is so enormous that it is impossible to give in detail all the work done. Many significant advances have been made, especially in the past year or two, and it is the purpose of this review to discuss the most important phases of the subject as it bears on pediatrics. The effect of the pituitary-like hormone, i.e., the pregnancy urine placental hormone, on sex development will be considered first and the sex hormones proper, such as androgen and estrogen, second.

GONADOTROPIC HORMONE IN PEDIATRICS

In 1927-1928 Zondek and Aschheim[1] discovered a gonadotropic hormone in pregnancy urine. Two years later Shapiro[2] reported that this hormone stimulated the sexual apparatus of sexually underdeveloped boys and young adults and that it caused the undescended testicles of young males to migrate into the scrotum. This discovery received a scientific backing in 1932 when Engle[3] demonstrated that the injection of gonadotropic substances in immature monkeys brought about a descent of the testes. These reports stimulated many clinicians[4-22] and physiologists to learn more about this gonadotropic hormone. The recent literature is of interest because enough publications have accumulated in the past decade to permit a preliminary evaluation of the possible benefits and dangers associated with the administration of pregnancy urine extracts.

Physiology of Pregnancy Urine.—Pregnancy urine extracts contain a protein substance which, because of its action on the gonads, is named a gonadotropic hormone. This pregnancy urine hormone is frequently referred to as the anterior pituitary-like (A.P.L.) hormone. F. L. Hisaw* prefers to name it P-U as the hormone is elaborated in the placenta (Collip) and is distinctly different both biologically and chemically from anterior pituitary hormones. Inasmuch as the substance is usually prepared from human pregnancy urine or from the human placenta, there is less tendency for it to develop antibodies or antihormones[23] when it is injected into human subjects than there would be if it were prepared from another animal species. This is important because antihormones, whatever their nature is, inactivate some hormones and render them ineffective.[24]

Collip and his associates were the first to demonstrate that pregnancy urine hormone is elaborated by the placenta. The evidence at hand strongly suggests that this hormone is a single substance.[25] Most of

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*Personal communication.

our knowledge concerning the specific action of the hormone comes from animal experimentation. It should always be remembered that the following investigations may be interpreted only in terms of the animal species specifically referred to. When the pregnancy urine hormone is injected into immature female rats, its action is chiefly to luteinize the ovaries.[26, 27] Its action on immature males is to stimulate the interstitial (Leydig) cells of the testicles.[28, 29, 30] The action of the hormone upon hypophysectomized animals is augmented by small amounts of anterior pituitary follicle stimulating hormone (FSH).[31]

Although earlier investigators[32] emphasized that the action of pregnancy urine in the male was solely upon the interstitial cells and that it had no gametogenic (sperm forming) activity, more recent investigations of Rubenstein,[33] Heckel,[34] and Brosius and Shaffer[35] show that pregnancy urine injections increase the number of spermatozoa of human adults. The male hormone elaborated by the stimulated interstitial tissue may act directly on the tubules. This may explain the gametokinetic action of pregnancy urine.

Most authorities assume that pregnancy urine stimulates the interstitial cells of the testicle to produce the male hormone; viz., androsterone, testosterone, and dehydroandrosterone, and that these in turn stimulate the accessory sexual structures to grow and mature just as they do when one of the androgens is injected alone. There is considerable evidence available for the correctness of this assumption. It is necessary in this connection to distinguish between the gonadotropic and the male and female sex hormones, androgen and estrogen. In the absence of a healthy ovary the former cannot produce estrus since it acts by stimulating the ovary to produce estrogen. Estrogen, on the other hand, can cause estrus directly in the absence of ovarian tissue. The gonadotropic action of pregnancy urine is the basis for the clinical administration of the hormone to boys and young male adults. With them, as with animals, pregnancy urine promotes primary growth of the testicles and secondary growth of the penis, prostate, seminal vesicles, and other accessory sex organs. If the gonadotropic hormone is given in large doses, premature puberty may develop.[36, 37, 38] Thompson and co-workers[36, 37] found that this could be prevented by keeping the period of treatment less than nine weeks. Overtreatment has been known to result in over-development of the penis. These findings seem to indicate that treatment should be carried on with caution and under close supervision in order to guard against excessive genital growth.

Clinical Applications.—Pregnancy urine is used to correct certain abnormalities of male sexual development. The commonest of these is cryptorchidism (undescended or ectopic testicle). It is important that the testis reach its normal scrotal position by the time of puberty because after that time the spermatic tubules tend to degenerate with consequent loss of fertility.[39] Furthermore, cancer is fifty times more frequent in undescended testes.[40, 41] There is some evidence that cryptorchid testes produce subnormal amounts of male hormone. In the human being, as in the animal, pregnancy urine stimulates the interstitial cells to produce male hormones,[42] enlarges the testicle, and, by some mechanism which is not clearly understood, stimulates it to descend into the scrotal sac unless descent is prevented by a mechanical barrier such as fibrous adhesions. The descent may be caused by the induced male hormone secretion. Hamilton has shown that testicular descent can be induced in immature

monkeys by injecting testosterone. Even in those cases in which complete descent of the testicle does not result, P-U therapy may render surgical replacement of the organ more successful by virtue of enlarging the genitals[43] and preventing postoperative atrophy.[44] P-U may also be useful in cases of sexual underdevelopment without cryptorchidism. On the other hand, a significant number of undescended testes migrate spontaneously to their normal position at the time of normal physiologic puberty.[40, 41] According to the combined figures of Nixon[45] and Bigler and co-workers[46] about nine out of every ten undescended testicles will have descended by the time the patient is twenty-one years of age. This conclusion is drawn from the difference in the reported incidence of cryptorchidism among children under twenty-one years and men over twenty-one years of age. For the younger group the incidence approximates 3 per cent, and for the older group, 0.3 per cent. The accuracy of the figures for children is probably open to doubt, since clinicians do not always distinguish carefully between pseudocryptorchidism and true cryptorchidism. The former is due to temporary physiologic spasm of the cremasteric muscles which draws the testicle out of the scrotum. This physiologic spasm may be overcome for diagnostic purposes by applying a hot water bag to the perineal region for a half hour prior to examination.[47]

The optimal age for hormone treatment is not yet clear. Most authors treat their patients between the ages of 6 and 12 years, and almost all agree that the testis should be in the scrotum before puberty. The question of dosage is also undecided. Some "successfully" treated patients have received as few as 100 rat units and others as many as 80,000 over periods of time ranging from a few days to several months. A factor which contributes further to the confusion is the difference in biologic tests which form the basis for rat units. Those interested in using P-U or other commercial hormone preparations can consult the investigations of D'Amour and D'Amour,[48] who found that several preparations contained considerably less than their labelled potency. A conservative plan of treatment is to give a total of 3,000 rat units of P-U over a period of six weeks. If the desired effect has not been obtained, the patient may be observed for three weeks and then given another course of treatment with a greater number of total units as indicated.

Excessive treatment with P-U may cause precocious puberty in boys. Thompson and others[36, 37] gave total doses of 55,020; 60,570; and 37,720 units of APL to three boys aged four, six, and nine years, respectively. They all showed increase in size of the penis, scrotum, and prostate, increased masculinity, a growth of pubic hair, and a change in the pitch of the voice. Plum[38] made similar observations.

The combined figures of Nixon[45] and Bigler and co-workers[46] suggest that the hormone therapy of cryptorchidism is successful in approximately 60 per cent of all cases. Some observers report a much lower percentage of success, while others contend that they have no failures. During the past year Thompson and co-workers[36] were successful in 22 per cent of their cases. Dorff[49] believes that hormone therapy caused complete scrotal descent in three out of twelve cases of intraabdominal cryptorchidism. To effect this he used up to 78,500 rat units of the P-U hormone and noted that the larger doses tended to cause precocious suprapubic hair growth. The hair disappeared after cessation of treatment in the younger age group. It seems probable that hormone therapy is completely satisfactory in about one-third of the cases of true cryptorchidism.

The ultimate effect of hormone therapy upon fertility is not known at the present time. MacCollum[39] has made a clinical study of the spermatogenesis of undescended testicles. Except in a small percentage of cases he finds the fertility of all persons with cryptorchidism to be lower than normal. He emphasizes that the cosmetic result of orchidopexy (surgical placement of the testicle in the scrotum) cannot be used as a criterion of fertility. He finds that 61 per cent of the patients who had had surgical orchidopexy were definitely fertile and 82 per cent were potentially fertile. Before hormone therapy can be finally accepted as a substitute for surgery, the end results of hormonal treatment must be compared with those obtained by the surgeon. The results reported by MacCollum are the only ones that we could find giving the status of the cases in a series after they had attained adult life. Sufficient time has not yet elapsed to permit gathering of similar data concerning those who have had hormonal therapy.

Hormonal therapy has added a useful means of treating cryptorchidism, and, unless latent harmful effects are discovered in the future, it can be considered as an acceptable method of treatment. Its application to other types of genital dystrophy needs further study.[43, 50, 51, 52]

SEX HORMONES

The Estrogenic Hormones.—The sex hormones may be divided roughly into two classes, the estrogens and the androgens. Both are steroid chemical substances, many of which have been prepared in chemically pure form. The estrogens are characterized by their ability to produce estrous cornification of the vaginal epithelium of rats and related animals. Estrone is one of the estrogens which is found in human urine and is the estrogen upon which the international unit is based. One-tenth gamma (1/10,000 milligram) of estrone is one international unit, which is approximately equal to one mouse unit. The rat unit used in this country is the equivalent of from 3 to 10 international units. Estradiol has been isolated directly from follicular fluid of the ovary and is twelve times more potent than estrone.

The sources of estrogens in the animal body have not been established with certainty. One major source is probably the theca interna of ovarian follicles of all sizes.[53] The intermediate metabolism of the estrogens is yet to be determined. The excretion of these substances is at present under extensive investigation. There are numerous methods for extracting and assaying sex hormones from the urine. Koch[54] emphasizes that many of these are unreliable. In a series of clinical papers he and his co-workers outline the methods they recommend.[55-57] The chief difficulty in the estimation and evaluation of urinary estrogens lies in the fact that such a hormone in the urine may be either free or combined. The free hormones have biologic activity, whereas the combined hormones are much less active and, being water soluble, are not extracted from the urine by the usual method. Until the significance of these two forms of the hormone is clear only tentative conclusions may be drawn from the clinical reports on estrogen excretion. The biologic methods of assay are based upon the reaction of an animal's generative tract to the hormone when it is administered over a measured period of time. This type of assay has the advantage of demonstrating that the substance has definite physiologic activity. There is another type of method which is based upon the formation of a colored chemical com-

pound.[58] The colorimetric methods (e.g., Venning et al.) are highly satisfactory for the estrogen of pregnancy urine, but none are as yet applicable to any other material. The biologic methods are therefore recommended for the present.

In 1929 Philipp[59] demonstrated that there was estrogen in the urine of newborn babies. Bruhl[60] was able to confirm this and to show that the hormone disappeared by the fourth day of life. Zondek and Euler[61] studied children from 6 to 11 years of age and found from 5 to 20 mouse units per liter. More recently Dorfman and his associates[62] by means of an improved extraction technique found much higher values in the urines of some children. Expressing their results in terms of international units of estrogen per 24 hours, they found that boys under 13½ years excrete between 9 and 48 units, whereas those between 13½ years and 16½ years of age excrete between 18 and 95 units. Oesting and Webster[63] present a smaller series of boys in whom they find the estrogen excretion to range between 10 and 60 international units per day. Their subjects were between 12½ and 15 years old. These preliminary observations indicate that there is a rise in the estrogen excretion following puberty. The data concerning girls are too small to be significant.

ESTROGEN IN PEDIATRICS

The knowledge acquired from animal experimentation has formed the basis for a method of treating vulvovaginitis in childhood. The normal vagina of a young girl is lined with a thin layer of epithelium which is susceptible to gonococcal infection. The mature adult vagina, on the other hand, is lined with a thick layer of epithelium which is supposed to be highly resistant to the infection. Lewis[64] noted these differences and inferred that estrogenic hormone might be effective in the treatment of childhood vaginitis if it caused the immature vaginal epithelium to thicken. In a small series of children treated with estrogen he reported that eight were cured and that only two suffered relapses. In the five years since Lewis' work was published, many other papers bearing on this subject have appeared.[65-75] These writers think that this type of treatment is an effective and safe form of treatment provided it is properly controlled. The actual percentage of cures reported varies with the standards set by the authors. Some have reported approximately 80 per cent cured, while others had less favorable results. It is still an open question as to whether beneficial results are due to anatomical changes in the vaginal epithelium or to changes in the hydrogen ion concentration of the vaginal secretions. In a recent paper Te Linde[74] has summarized the results he obtained in a series of 175 cases. He recommends that a vaginal suppository containing from 600 to 1000 international units of estrogen be inserted daily for about thirty days. Using this dosage he finds that the vaginal epithelium becomes thickened in fourteen days and that vaginal smears become negative in eighteen days. If estrogen is used, it is essential that the patient be seen at least once a week. Treatment should be stopped if signs of sexual precocity, such as pubic hair or development of the breasts, appear.

Corpus Luteum Function.—Until the last year, attempts to assay the corpus luteum hormone, progesterone, in the body tissues and fluids have met with poor success. Progesterone is the hormone which is produced by the ovary after the follicle has matured and discharged its ovum. If impregnation does not take place, the corpus luteum degen-

erates and shrinks just before the next menstrual period, whereas in pregnancy it grows and lasts for several months. The isolation of sodium pregnanediol glucuronidate, the physiologically inactive end product of progesterone, from human pregnancy urine by Venning and Browne[76-79] is probably the explanation for the previous failures to detect this hormone in any quantity. Venning[80] has published a quantitative method for extracting the pregnanediol compound from the urine and has presented further experimental proof[81] that progesterone is excreted as pregnanediol glucuronidate. She finds that the uterus is a necessary factor in the conversion of progesterone to its end product. Inasmuch as the excretion compound appears in the urine twenty-four to forty-eight hours after ovulation, its measurement offers a new method of investigating the sexual development and physiology of adolescent girls.

Androgens.—These are the so-called male hormones which are substances characterized biologically by their ability to promote growth of the capon's comb and mammalian penis, seminal vesicles, etc. In other words, the androgens stimulate the male accessory genital structures. The quantities of androgen are usually expressed in terms of international units. One unit is equal in activity to 0.1 mg. of androsterone. It is probable that the interstitial (Leydig) cells of the testicle are the chief source of this hormone in normal individuals. There may, however, be extra gonadal sources, such as the adrenal.[82] There is also evidence which suggests that the adrenal may produce estrogenic hormone.[83] The androgens appear in the urine in both combined and free forms. As with the estrogens, it will be difficult to evaluate urinary findings until the metabolism of the male sex hormones is more clearly understood.

There are two types of assay in general use for the determination of urinary androgens. The first is biologic and depends upon the reaction of some animal organ, such as the capon's comb, to administered hormone. Koch[54] and co-workers[55, 57] recommend the comb growth method; the other type of method depends upon a color reaction.[84-87] To quote Wintersteiner and Smith,[88] "The lack of correlation between the colorimetric values and bioassay results, apparent in the data of Oesting, would not seem to recommend the method in this particular form for anything but a very rough estimation of the male hormone content of urine."

Dingemanse and co-workers[89] find 15 units of androgen per liter in boys, while in adult men they find 40 to 50 units per liter with extreme variations of from 15 to 170. Detailed information is now available on the daily excretion of androgens in normal individuals of both sexes through the efforts of Gallagher and his associates.[56] There is no evidence of a cycle in the excretion of androgens in males or females, although there is definite evidence of a cycle in the excretions of estrogens by females. There is marked fluctuation in the day-by-day androgen and estrogen output. Dorfman and associates[62] report that the androgenic activity (in international units) rises in proportion to physical maturity. Boys under 13½ years excrete between 1.1 and 15 units, while boys over 13½ years excrete between 6.0 and 32 units. In a small group of girls between the ages of 7 and 12 years, they report a daily excretion of from 0.7 to 7 units. Oesting and Webster[63] report androgen excretion in terms of color units (= 0.1 international unit). Boys between 3 and 8 years have an androgenic output per twenty-four hours of from 24 to

120 C.U.; between 8 and 12½ years, from 56 to 187 C.U.; and between 12½ and 15 years, from 128 to 300 C.U. Girls tend to have a slightly lower androgen output when compared with boys of corresponding age.

Sex Hormone Excretion in Sexual Endocrine Disturbances.—Koch and his group[57] find that male castrates exerete very small amounts of gonadal hormones. In another group of males with hypoplastic genitals and accessories, poor ejaculation, retarded secondary sex characteristics, and delay in the closure of the epiphyses, the androgen output was about one-third normal, and the estrogens were reduced to traces. Observations on a 13-year-old cryptorchid boy reveal that his urine contained only traces of androgenic material, whereas in the case of another cryptorchid patient of 26 years whose secondary sex characteristics were normal, the androgen excretion was normal. Very high levels of androgen excretion were observed in cases of adrenal virilism.

Observations by other authors include a case of feminization in a male adult with carcinoma of the adrenal cortex.[90] Their patient excreted an excess of estrogenic hormone which disappeared after operative removal of the tumor and reappeared with recurrence of the growth. Butler and Marrian[91] have isolated a steroid compound from the urine of women showing the adrenogenital syndrome. The excretion of this substance seems to be associated with the syndrome. Loeb and his colleagues[92] have also studied the nature of urinary hormone excretion in cases with adrenal cortical tumors. These investigations suggest that hormone studies may become an essential item in the accurate diagnosis of sexual abnormalities.

The application of the newer knowledge of the physiology of the sex glands to clinical practice is still in its infancy. The use of these methods of study will be limited because of their expense until they become simplified and can be generally applied to many types of conditions. They offer interesting methods of study which may develop important new principles and change the conception and treatment of many of the endocrine conditions.

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American Academy of Pediatrics

Proceedings

MEETING OF THE EXECUTIVE BOARD OF THE AMERICAN ACADEMY OF PEDIATRICS

The meeting of the Executive Board of the American Academy of Pediatrics was held November 27, 1938, at the Orrington Hotel, Evanston, Ill., with the president, Dr. Henry F. Helmholz, in the chair and the following members present: Dr. Joseph B. Bilderback, vice-president; Dr. Clifford G. Grulee, secretary; the regional chairmen, Dr. Stanley Nichols, Region I, Dr. E. C. Mitchell, Region II, Dr. A. Graeme Mitchell, Region III, Dr. Edward B. Shaw, Region IV; and the associate chairmen, Dr. Edgar E. Martmer and Dr. Hugh K. Berkley.

The following were elected to Fellowship:

Region I

Dr. Robert S. Buol, New Britain, Conn.
Dr. Nathan H. Einhorn, Philadelphia, Pa.
Dr. Geoffrey W. Esty, Westfield, N. J.
Dr. Albert Guilbeault, Montreal, Que., Can.
Dr. Marvin Israel, Buffalo, N. Y.
Dr. Paul Letondal, Montreal, Que., Can.
Dr. Milton I. Levine, New York, N. Y.
Dr. Samuel Z. Levine, New York, N. Y.
Dr. Rosa Lee Nemir, New York, N. Y.
Dr. Wallace J. Nichols, Medford, Mass.
Dr. Herbert C. Soule, Rochester, N. Y.
Dr. Lewis K. Sweet, Washington, D. C.
Dr. Percival E. Williams, Hamilton, Ont. Can.

Region II

Dr. Charles B. Etter, Memphis, Tenn.
Dr. William O. Vaughan, Nashville, Tenn.

Region III

Dr. Harry H. Boyle, Chicago, Ill.
Dr. Benjamin W. Carey, Jr., Detroit, Mich.
Dr. Harry O. Davidson, Detroit, Mich.
Dr. Jerome Diamond, St. Louis, Mo.
Dr. Dennis D. Kovan, Detroit, Mich.
Dr. Daniel B. Landau, Hannibal, Mo.
Dr. Walter C. McKee, Chicago, Ill.
Dr. Merle D. Pierson, Detroit, Mich.
Dr. Lewis P. Sonda, Detroit, Mich.

Region IV

Dr. William C. Black, San Diego, Calif.
Dr. Chester I. Mead, Bakersfield, Calif.

Emeritus Fellowship was granted to the following:

Dr. Harry C. Berger, Kansas City, Mo.
Dr. Irving A. Frisch, Hollywood, Calif.
Dr. Eugene Rosamond, Memphis, Tenn.

The resignation of Dr. Donald W. Porter, of New Haven, Connecticut, was accepted with regret.

The Treasurer's report was accepted and the annual budget considered and approved. It was decided that in view of the fact that the annual meeting hereafter would be in the fall it would be necessary next year to hold a meeting of the Executive Board in the spring, the time and place to be decided upon by the Secretary.

Dr. Lewis Webb Hill of Boston, Massachusetts, was appointed Associate Chairman for Region I.

The appointments of the following state chairmen were announced by the president:

Region II: Georgia, Dr. W. L. Funkhouser, Atlanta
Region III: Michigan, Dr. Wyman C. C. Cole, Detroit
Missouri: Co-chairman, Dr. Hugh L. Dwyer, Kansas City

Dr. Thomas B. Cooley, executive secretary of the Council for Pediatric Research, was present and discussed the problems and outlook of the council for the future. The work of this group has been going on steadily; much progress has been made; and it is hoped that certain projects under consideration will prove of value.

The report of the Committee on Contact Infections was read and approved. This committee recommended essentially that the various activities which it had promulgated in its former efforts should be continued and intensified. In connection with this committee's work, the secretary was instructed to send an official letter of thanks to Mead Johnson & Company for supplying the leaflets, "For the Sake of the Children."

The report of the Committee on Cooperation with Nonmedical Groups and Societies was read and approved. Dr. Joseph H. Johnston, of Detroit, was added to this committee at the request of the chairman. The report detailed the meeting of a group from the committee with the representatives of the American Camping Association and also with Dr. Lillian Smith, representative of the Parent-Teacher Association, who asked that the Academy cooperate in the summer round-up of that organization. A discussion of more careful examination of school children was taken up at this time. The recommendations of the committee were followed in this respect.

1. A committee to cooperate with the American Camping Association to be known as a Committee on Medical Supervision of Camps. The following committee was appointed:

   Chairman, Dr. Warren Sisson, Boston, Mass.
   Dr. W. L. Funkhouser, Atlanta, Ga.
   Dr. Roger L. J. Kennedy, Rochester, Minn.
   Dr. Vernon W. Spickard, Seattle, Wash.
   Dr. Henry E. Utter, Providence, R. I.

2. Further cooperation with the Parent-Teacher Association (approved).
3. That active committees be developed in each state to assist in the activities of this committee (approved).

The report of the Committee on Hospitals and Dispensaries was approved. This committee was authorized to proceed with a survey to determine what precautions are taken by various pediatric hospitals to protect their patients from contact infections.

The report of the Committee on Infantile Paralysis was accepted and approved, as was that of the Committee on Immunization Procedures.

The report of the Committee on Pediatric Awards was approved.

The report of the Committee on Mental Hygiene was approved. The recommendations of this committee stressed adequate training of the pediatric interne and

resident and the publication of articles in THE JOURNAL OF PEDIATRICS and elsewhere, for increasing interest in this subject. The question of combining such articles into a pamphlet to be given to the members was discussed.

The report of the Committee on Neonatal Morbidity and Mortality was read and approved. It was voted to allow expenses up to $150 to promote a meeting of this group with like groups from other organizations.

The report of the Committee on Nursing Education in Pediatrics was read and approved. The resignation of the chairman, Dr. A. Graeme Mitchell, was accepted, and Dr. Merlin Cooper, of Cincinnati, Ohio, was appointed chairman.

The report of the Committee on Revision of the Pharmacopoeia was accepted. Of the three main recommendations of this committee, the first, to promote the publication of a pediatric therapeutics and formulary, was not thought feasible at the present time. It was voted to apply for representation on revision of the *United States Pharmacopoeia* and the *National Formulary*. It was felt that the action of the committee in soliciting and editing articles on pediatric therapeutics, to be published in the various journals, was commendatory. The Executive Board did not feel, however, that it could take part in promoting a "Pediatric Pharmacy Week."

The report of the Committee on School Health and School Health Education was approved by the Executive Board and that committee was heartily commended for its activities and enterprise. It was thought that the work of this committee could be further developed by appointing state committees to work through the national group.

It was decided, on request of the chairman, to discontinue the Committee on Cooperation with Medical Groups and Societies.

The Committee on Medical Education felt that there was nothing urgent to report at the present time since the American Board of Pediatrics had been established, and there was being carried on a study of graduate education which would materially influence the action of this committee.

The Committee on Legislation had no matters referred to it during the past year. The same was true of the Committee on Clinical Investigation and Scientific Research.

The report of the Committee on Child Health Relations was read and approved. The resignation of the chairman was accepted with regret, and Dr. Stanley H. Nichols was appointed to replace Dr. M. Hines Roberts.

There was some discussion of the next annual meeting to be held in Cincinnati, Nov. 16, 17, and 18, 1939; further discussion of which was deferred until the next meeting of the Executive Board.

The president was authorized to appoint a committee of three as a program committee to assist the secretary in developing programs for future annual meetings.

It was voted that at future annual business meetings the incoming president shall take the chair and the outgoing president shall present the agenda of the Executive Board meeting.

The secretary was authorized to turn over to the treasurer of the American Committee of the International Congress of Pediatrics, upon his request, any money that had been collected by this Society for that congress.

It was the consensus of opinion that while the scientific meeting of the Academy in 1940 should be replaced by that of the International Congress of Pediatrics, at least a one-day business meeting should be held previous to, or immediately following, that congress.

Dr. Bret Ratner suggested that we develop a section on allergy in the Academy. After discussion the Executive Board felt that it did not care to make this departure at the present time.

It was decided to send official invitations to certain of our colleagues in adjoining countries, especially Cuba, to meet with us at the next annual meeting.

After full discussion of the possibilities, the Executive Board decided to employ Mr. Lawrence H. Selz, of Chicago, to take care of publicity for the Academy for the year, 1939.

The Executive Board approved the following proposal of Dr. Albert D. Kaiser, which was recommended by the state chairmen of Region I: "In view of the well-established fact that the child with cardiac disease is a cripple in every sense of the word, it is the consensus of opinion of the assembled pediatricians of Region I of the American Academy of Pediatrics that the cardiac cripple should be given medical, hospital and convalescent care by the State Agency responsible for the program of services to crippled children."

The Executive Board approved the pamphlet entitled, "A Study of the Minimum Desirable Standards for the Health Supervision and Care of Infants and Children," presented by Dr. Stanley Nichols as coming from the members of the Academy in New Jersey; the secretary to investigate the question of publication and be empowered to publish this under proper circumstances.

The Executive Board recommended the following change in the By-Laws:

Article II. Section 3—second paragraph—which reads as follows:

"The associate regional member shall be appointed by the President of the Academy from a group of two or more candidates nominated by the state chairmen of the regions"—that the words, "and recommended by the Executive Board," be added.

EIGHTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

DEL MONTE, CALIF., JUNE 9, 1938

Round Table Discussion on Convalescent Serum Therapy

Chairman: Dr. Clarence M. Hyland, Los Angeles, Calif.
Assistants: Dr. James A. Conner, Chicago, Ill.
Dr. Sidney O. Levinson, Chicago, Ill.
Dr. F. M. Meader, Detroit, Mich.
Dr. William Thalhimer, New York, N. Y.

The Convalescent Serum Center and Its Relation to the Community

Clarence M. Hyland, M.D.

The purpose of this Round Table Conference is to discuss the results which have been observed from the use of convalescent serum in the control of scarlet fever, measles, mumps, chicken pox and whooping cough, also its more recent employment in the treatment of pneumonia and diverse streptococcus infections.

Your chairman wishes to express grateful appreciation to Dr. Conner, Dr. Levinson, Dr. Meader, and Dr. Thalhimer, pioneers in this work, for their participation in this discussion.

Since we are dealing with a comparatively new and very valuable type of treatment, and in view of the fact that methods of control of certain contagious diseases by convalescent serum are not as universally recognized as they should be, your chairman feels that a portion of this meeting should be given over to a discussion of the Serum Center, including a brief account of its methods of obtaining a supply of serum and its value to the community. It seems that the function of the Serum Center should not stop with providing a continual supply of convalescent serums but that it should assume an important role in the education of the general medical profession and the public in the use of these serums.

Such an educational program must necessarily be confined to the state or surrounding territory in which the center is located, but the increasing value of the serum center to the community and state would manifest itself in a lowered morbidity and mortality rate from contagious diseases especially among infants and young children.

Unfortunately only a few of the larger cities have serum centers where convalescent serum is available to private practitioners as well as for hospital use. There are a growing demand for serums and a need for the establishment of new centers in the various states, preferably in connection with contagious disease hospitals, well-equipped hospital laboratories, special convalescent serum laboratories, or in association with a department of health.

Convalescent serum, as the name suggests, is obtained from the blood of recent convalescents; it may be collected and stored in a refrigerator until needed. In collecting a supply of serum, names of persons recently recovered from the various diseases are secured, and these individuals are solicited regarding the withdrawal of a quantity of blood for which a proper fee is paid. The consent of the attending physician should always be obtained before any solicitation of the patient. We have found at the Children's Hospital Convalescent Serum Center that this permission has been granted in many thousand instances without a single refusal on the part of the physician.

Blood may be obtained in a contagious disease hospital, by advising the patient of the value of this therapy and furnishing serum with the understanding that on discharge, or before, the patient make a donation of blood to pay for the serum used. I know that this method has operated very successfully in at least two contagious units. Slightly more serum may be obtained from one bleeding than is used in the treatment of the case. In this way a considerable stock of serum may be collected.

In order to insure a high antibody content, bleedings should be made relatively early after recovery; multiple bleedings may be made on the same donor provided not more than an average of 100 c.c. of blood per week is exceeded. Fasting donors only should be bled in order to reduce the number of lipemic serums to a minimum. In the procedure a small amount of novocain is injected over the selected vein, and bleeding is accomplished by means of a suitable bleeding set. The removal of the blood is painless and without ill effect as shown by the bleeding of several thousand immune donors. The blood is placed in the icebox overnight, and the serum is removed the following day.

Individual bulk serum is cultured and tested by both the Wassermann and Kahn methods, and, if at the end of a week the cultures are negative and the Wassermann and Kahn tests are also negative the serum is stored without preservative and held in this state until a demand for its use is anticipated.

As needed, twenty or thirty or more bulk serums are added together in a pool and filtered; a preservative is added, and the serum is transferred to suitable sized ampoules. Cultures are taken of the pool and of a certain number of the final containers, and a portion of the serum is reserved for injection into an animal. The product is considered suitable for use if the cultures are negative after an incubation period of one week and if the injected animal shows no toxic symptoms within this period.

If proper caution is observed in the sterilization of all equipment and if procedures having to do with the final product are conducted by skilled workers in dust-free rooms, contaminations are virtually unknown.

Due to the expense of human blood the cost of human convalescent serum is somewhat in excess of the universally used antitoxins. One who has by personal contact observed the remarkable and many times dramatic results from this type of treatment sees without question full justification for the production and use of convalescent serum.

I have in mind a large contagious disease hospital using scarlet fever serum and saving in hospital days care more than enough to pay for the serum used. This is possible because of the more rapid recovery of the serum-treated case and the reduction of complications 50 per cent or more.

It is clear therefore that the technical part of this work may be accomplished without serious difficulty in any well-conducted laboratory by setting aside a small unit of space and adapting it to this purpose.

Pediatricians, more than any other medical group, fully realize the dangers of measles in the young and subnormal child, and they are also cognizant of the large percentage of complications and higher death rate from scarlet fever in the younger age groups, as indicated by their activity in promoting the use of convalescent serum in these diseases, wherever it is available.

I am sure you will lend your support and advice toward the establishment in your community of a central source of supply to the end that the various convalescent sera may be made readily available. I can assure you from personal experience in the establishment and operation of one of the larger centers that

serum centers pay large dividends to the sick of your community and when once established they occupy a prominent place in the public health affairs of that community.

The Prophylactic and Therapeutic Use of Convalescent Serums: Scarlet Fever, Mumps, and Chicken Pox

William Thalhimer, M.D., Serum Laboratory, New York City

During the past year, the second year of the convalescent serum laboratory, the demand for convalescent scarlet fever serum in the Greater New York area has been double that of the first year. Again, as was my experience in Chicago and Milwaukee, when convalescent serum became available in adequate amounts to physicians and to infectious disease hospitals, they preferred to use convalescent scarlet fever serum for treatment and prophylaxis instead of scarlet fever antitoxin. This is also the attitude of internes and residents in infectious disease hospitals. In fact, some physicians today refuse to use antitoxin at all; apparently they have several reasons for this. They have found convalescent serum efficient when proper doses are used; they have found its use practically free from the risk of serious reactions, of causing serum sickness, or of producing sensitization since the few reactions that do occur are mild ones and do not cause any serious concern. Also, they have verified our recommendation that in the treatment of scarlet fever convalescent serum injected in adequate amounts intravenously will give rapid and excellent results.

The choice of the intravenous route of injection of convalescent scarlet fever serum for therapy should be stressed. This principle is well recognized in the treatment of all patients severely ill with any infectious disease. The reasons for this are quite simple. Under these conditions it is important that the therapeutic serum should be distributed throughout the blood stream and the entire body as rapidly as possible. It is obvious that the only way in which the entire amount of serum injected will appear immediately in the blood stream is by injecting the serum into the blood stream. It takes longer than is usually realized for serum, even homologous serum, injected subcutaneously or intramuscularly, to be completely absorbed.

In an experimental investigation carried out with A. Levinson and Katharine Howell and Catherine Wilson, which will be published soon, we studied in rabbits these different rates of absorption of homologous and heterologous serums. Five minutes after intravenous injection of serum, specific antibodies were present at maximum titer in exactly the dilution calculated on the basis of the amount of serum injected and blood volume of the animal. The titer of the antibodies studied, agglutinins and hemolysins, did not decrease in these normal animals until after twenty-four hours, diminishing slowly, so that even two weeks later a low titer was present. When the same amount of serum was injected into the muscles of the hind leg, it took from fourteen to sixteen hours, on an average, for the maximum titer to appear in the blood, and its level then was only half that found five minutes after the intravenous injection of the same amount of serum. The titer began to diminish from this lower level twenty-four hours after the serum was injected. It would appear, therefore, that the intravenous injection of serum is the method of choice, and no advantage is to be gained by following an intravenous injection with subsequent intramuscular injections. When multiple injections are indicated, the advantage is entirely in making each injection into the vein.

Our therapeutic results in scarlet fever from the intravenous injection of convalescent scarlet fever serum continue to be of the same order as those reported previously with Hoyne and S. O. Levinson, and by others.

When treatment is instituted within thirty-six hours after the onset of scarlet fever the disease is aborted in twelve to eighteen hours in 65 per cent of the patients, the temperature becoming normal, toxemia disappearing, the rash either fading or disappearing, and desperately ill patients being converted into convalescing ones. In the other 35 per cent the benefit is not so rapid because, as a general rule, of the existence of complications at the time the serum is given. Nevertheless, even under these conditions, the results are well worth while, although at times the complications, such as sinusitis and mastoiditis, are stubborn, and the latter may require operation. Experience has demonstrated that convalescent serum, when given early to individuals free from complications at the time, will reduce the likelihood of the development of complications to one-third, and the complications that do develop will be less severe. The results indicate that convalescent scarlet fever serum is more efficient in preventing complications than antitoxin. Some of the complications which are present when serum is given, such as arthritis, disappear rapidly. Cervical adenitis usually clears up much sooner than is expected. However, sinusitis, middle ear infections, and mastoid infections many times run their usual course.

A discussion of the treatment of scarlet fever is not complete today without mentioning the therapeutic trial of the remarkable new drug sulfanilamide. Although sulfanilamide has caused many remarkable recoveries in various kinds of severe hemolytic streptococcal infections, and in infections with other organisms also, the local experience in the New York area is that sulfanilamide has either no beneficial, therapeutic action on scarlet fever or at most, a questionable one. Similar negative results have been published by other workers.

Apparently sulfanilamide is of some aid in the treatment of some of the complications of scarlet fever, but it is peculiar that even here the improvement obtained is not as marked as might be expected from the use of sulfanilamide in other kinds of streptococcal infections, such as meningitis and peritonitis. At times the administration of sulfanilamide has other disadvantages in addition to its toxicity for some individuals.

Dr. Karelitz has consented to let me tell of a patient of his, a child who developed signs of mastoid involvement complicating scarlet fever. The child first had a streptococcal pharyngitis, an infected middle ear, and slight mastoid tenderness, for which sulfanilamide was given. Paracentesis of the ear was followed by profuse discharge. Soon afterward a rash appeared, typical of scarlet fever, but there was the possibility that it was a sulfanilamide rash. With the intravenous administration of convalescent serum the rash and scarlet fever rapidly cleared up. Discharge from the ear, the mastoid signs and temperature persisted. With sulfanilamide all of these symptoms diminished. As soon as the administration of sulfanilamide was stopped, all symptoms reappeared promptly, especially a profuse purulent discharge from the ear. With the readministration of sulfanilamide again all symptoms decreased for a few days, only to reappear again when the drug was withdrawn. At this time the mastoid tenderness was so apparent that a roentgenogram was taken which indicated extensive mastoid disease. Operation was performed immediately and revealed marked involvement and destruction of the mastoid. This was followed by a smooth convalescence and recovery. Later the child desquamated proving that he had had scarlet fever. Apparently sulfanilamide in this patient did not check the mastoid involvement, but merely covered up the signs and delayed the operation. A second similar experience was related to me by another physician.

We have had some instances showing that the synergistic effect of convalescent serum and sulfanilamide in treating some of these complications of scarlet fever is similar to the evidence we have had of the synergistic action of these two agents in the treatment of severe hemolytic streptococcal infections other than those caused

by scarlet fever, such as hemolytic streptococcal pneumonia. These results are similar to the experimental results of Rosenthal and his co-workers.

Usually only one intravenous injection of convalescent serum is necessary when administered within thirty-six hours of the onset of scarlet fever, especially if no complications are present at the time. When given later, after complications have appeared, several injections are usually necessary. The intravenous doses recommended early in scarlet fever are 20 c.c. in children up to the age of 5 years, 40 c.c. in children from 5 to 10 years, 60 c.c. from 10 to 15 years, and 80 to 100 c.c. in larger adolescents and adults.

The Schultz-Charlton blanching reaction produced with 1 c.c. of convalescent scarlet fever serum injected intracutaneously is extremely reliable in differentiating between a scarlet fever rash and rashes from other causes. It is definitely more certain, and in a larger percentage of cases, than is the same test carried out with scarlet fever antitoxin. Again, there is the advantage of the human serum in avoiding reactions or sensitizations. This serum is put up in 1 c.c. ampoules to be used for this test.

Our experience in the prophylaxis of scarlet fever with convalescent serum has been the same as that previously reported. To accomplish this the serum need not necessarily be injected intravenously; instead, it can be given intramuscularly. The prophylactic doses we recommend are 10 c.c. for smaller children, 15 c.c. for larger children, and 20 c.c. for adolescents and adults. With these doses scarlet fever is prevented entirely in 97 per cent of all of the children receiving the serum, and in about 85 per cent of those children that experience has shown are expected to develop the disease.

Although these amounts of serum will prevent the disease in these high percentages, positive Dick tests will not be converted into completely negative ones in the same percentage. This seems to us very interesting, and it would seem that the prophylactic efficiency must be due to antibodies and protective substances, in addition to erythrogenic antitoxin present in convalescent serum.

Dr. Elizabeth Moore, collaborating with me, has found that different pools of convalescent scarlet fever serum as we prepare them contain only from 5 to 10 units of erythrogenic antitoxin per cubic centimeter. These results are of the same order as those reported by Rhoades and as found in an unpublished study by S. O. Levinson and Clarice McDougall. Dr. Coburn has kindly consented to allow me to mention that he has regularly found from 300 to 600 units of antistreptolysin in the same pools of serum. This amount of antistreptolysin is consequently larger than that found in scarlet fever antitoxin.

Dr. Moore also has been studying with me the bactericidal power of convalescent scarlet fever serum for streptococci under certain experimental conditions. In brief, this has been an investigation of the increase in the bactericidal power of fresh defibrinated blood for hemolytic streptococci when convalescent serum has been added to the mixture of blood and organisms. The hemolytic streptococcus used has been one known as the "New York 5 Strain." Many convalescent sera, some obtained even as long as six months after the onset of the illness, have markedly increased the killing power of whole blood against this streptococcus. This strain, although an excellent toxin producer, is now relatively avirulent. We are now also working with recently isolated, virulent streptococci from various sources.

Because of these results, if generalized streptococcal peritonitis, pleurisy, or empyema is present, the direct injection of sizeable amounts of convalescent scarlet fever serum into these cavities might be of real aid in killing off the streptococci. It is my belief that this should be tried and that it can be done so with safety. With the proper technique it has been proved safe to inject serum into the peritoneal cavity, even a horse serum.

Banks, for example, regularly administers scarlet fever antitoxin intraperitoneally in treating children with scarlet fever, since he is afraid, because of the possibility of severe reactions, to inject this horse serum intravenously. He reports having injected the serum intraperitoneally into 540 scarlet fever patients with excellent results, comparable to those after intravenous therapy, with no accidents or bad results, not even pain. There was no pain when serum which did not contain phenol was used. The only preservative in our serum is $\frac{1}{10.000}$ merthiolate (Lilly).

I was able to persuade one physician to inject some convalescent scarlet fever serum intraperitoneally in the presence of a generalized hemolytic streptococcal peritonitis. The patient was almost moribund when this was carried out, so that benefit could hardly be expected. However, there was no deleterious effect whatsoever.

It recently has been shown that hemolytic streptococci of various origins, including scarlet fever, produce under different conditions a number of toxins different from the erythrogenic one. Some of these have been demonstrated in the work of Mudd, Todd, Hare, and Schlüter. Some of these toxins are extremely potent and are lethal to mice in minute amounts. A study of antitoxins for these recently found toxins is being carried on by a number of workers, and we hope to follow them in convalescent serum.

Tunnicliffe has demonstrated that opsonins for hemolytic streptococci are present in convalescent serum in relatively large amounts.

Scarlet fever antitoxin and other types of scarlet fever antisera prepared in the horse can contain only antibodies to whatever antigenic substances the horse has received. Convalescent scarlet fever serum, however, contains all of the substances which have been produced by a patient who has recovered from the clinical disease, scarlet fever. A number of workers have demonstrated various streptococcal antibodies in convalescent serum, which, it seems to me, could be expected. It might be that the efficiency of convalescent serum, which many observers believe to be greater than that of scarlet fever antitoxin in both curing scarlet fever and reducing the likelihood of complications, is caused by a number of antibodies present in convalescent serum, and not in scarlet fever antitoxin.

Mumps Convalescent Serum

The results with mumps convalescent serum have been surprisingly good. Although this serum has been used in a larger number of instances, we have complete reports on its use in 45 children up to 15 years of age. In only one did mumps develop, and, whereas the disease was not modified, no complications developed. The amount injected intramuscularly was 20 c.c.

In one instance the experience was quite conclusive. Thirty-six boys from 12 to 14 years old at a boys' camp were exposed to 3 boys with mumps. Eighteen boys previously had had mumps and did not receive serum; of the other 18 who had no previous history of mumps, 16 received serum and 2 did not because their parents refused permission. Only the 2 boys who did not receive serum developed mumps.

Twenty-three adults received prophylactic injections of mumps convalescent serum, most of them 40 c.c. intramuscularly. One woman, seven months pregnant, developed mumps with no complications and without interrupting pregnancy. A full-term, normal baby was born and did not develop mumps. Two adults developed mumps which, however, was mild and definitely modified, without complications. The other twenty did not have mumps.

Whereas mumps is not as infectious as either measles or chicken pox, these results indicate a very marked prophylactic efficiency of the serum. Still more extensive data, which have not been included, indicate the same degree of protection.

We have not had enough experience to know whether convalescent serum administered after the disease has started will prevent complications. We do know, however, that large doses of the serum, from 40 to 60 c.c., will alleviate complications, such as orchitis or oophoritis. We also do not know if the serum will lessen the severity of the parotitis, or shorten the course of the disease.

Chicken Pox Convalescent Serum

The results with the use of chicken pox convalescent serum are paradoxical. Our results indicated early in the study that even with small children an injection of 20 c.c. of serum was insufficient to prevent or modify the disease. From then on we used 40 c.c. amounts intramuscularly.

Although a large number of exposed children received the serum while in the hospital, we were able to follow completely only 59. Of these, 15 developed chicken pox, or 25+ per cent. Of 91 children observed in the hospital who did not receive serum and who were followed completely, 15 developed chicken pox, or 16+ per cent. This statistical study indicates, therefore, that chicken pox convalescent serum has no prophylactic efficacy. However, paradoxically, some of the children who received serum developed only extremely mild, modified chicken pox, with temperature not above 100° F. and with very few scattered typical lesions; the disease lasted only two or three days, including disappearance of crust. In these children there can be no doubt that the serum modified the disease. Also, some of the children receiving serum did not develop the disease, whereas the controls not receiving serum did. This is presumptive evidence that the serum prevented the disease in some. It is clear from this study that, whereas the serum in all probability has some efficiency, it is small compared with that of measles convalescent serum in preventing measles.

Also, it is evident that a dose of less than 40 c.c. is useless. Because of the large dose necessary, even granting that the serum has some efficiency, enough convalescent chicken pox serum could not be obtained to make its wide use practical. Nevertheless, the results are sufficiently suggestive to indicate that a sick or undernourished child, exposed to chicken pox, should be given the benefit of receiving 40 c.c. of convalescent chicken pox serum.

The Treatment of Hemolytic Streptococcic Infections With Human Convalescent Serum

Sidney O. Levinson, M.D.

Clinical reports are increasing on the use of pooled human convalescent serum in the treatment of hemolytic streptococcic infections. Since a previous publication by Thalhimer and myself, there has been an opportunity to observe and analyze reports on the results of the use of serum in several hundred cases. Experience with the use of serum has taught both its value and its limitation. The cases have been separated into three groups to illustrate these features. Interesting or characteristic cases from each group are presented.

I. *Acute Hemolytic Streptococcic Throat Infections*

Case 1.—E. K., 14 months old. After a low grade temperature and coryza of one week's duration, the child was admitted to the hospital with a temperature of 104° F. The throat was markedly inflamed and edematous. Membranous patches were present over the pharynx. The infant was markedly prostrated and dehydrated. Forty cubic centimeters of convalescent serum was administered intravenously at the height of temperature. There was an immediate critical drop, the temperature reaching normal in thirty-six hours. Coincident with this fall in temperature, the toxicity disappeared,

and there was general improvement in the symptoms with rapid recovery and discharge from the hospital three days after admission.

In this group of acute streptococcic throat infections with or without cervical adenitis, the response to convalescent serum is almost as specific and as striking as is seen in the treatment of early scarlet fever.

II. *Fulminating Hemolytic Streptococcic Infections of the Throat, With Septic Complications*

CASE 1.—V. P., aged 12 years. Three weeks before admission to the hospital, this child developed an ulcerative pharyngitis with a high temperature. Within two days a marked cervical adenitis appeared; the gland was incised after one week, but no pus was obtained. Although the adenitis gradually subsided, the septic temperature continued until three days before admission, when pain in the left shoulder appeared.

On admission the child was acutely ill and had a diffuse, soft, very tender swelling over the anterior left chest in the region of the second and third ribs and extending under the left axilla. A blood culture taken on admission gave a growth of hemolytic streptococcus. X-ray examination showed no evidence of osteomyelitis.

Three days following admission 60 c.c. of pooled convalescent scarlet fever serum was administered intravenously. The following day 180 c.c. of blood from a convalescent scarlet fever donor was given. One-half hour after the transfusion the child developed a chill and a temperature rise, which was interpreted as a transfusion reaction. There was a critical drop in temperature, with only one rise over 101° F., forty-eight hours later, and marked improvement. A blood culture taken the day following the transfusion was negative. The child made an uneventful convalescence.

CASE 2.—J. G., aged 7 years. Three weeks previously the child developed an acute pharyngitis, fever, and malaise. Eleven days after the onset of illness, both eardrums ruptured, draining pus. The temperature became septic in character, and the child was admitted to the hospital.

On admission, in addition to the findings of acute sepsis, there was evidence of involvement of the mastoids. Three days after admission, a right simple mastoidectomy was performed, revealing pus and a perisinus abscess. The following day a left simple mastoidectomy was performed, with the finding of pus in the antrum. The septic temperature continued, and the prostration became more marked. Six days after admission a blood culture was positive for hemolytic streptococcus. The patient pursued a downhill course, and on the eighth day after admission a right jugular ligation and a sinus exploration were performed. At this time, 200 c.c. of blood and 40 c.c. of scarlet fever serum were given intravenously. The following day another 40 c.c. of serum was given intramuscularly. This was followed again by 40 c.c. intravenously the following day. Although the temperature continued septic, the child's downhill course appeared to have been checked. The following day, 200 c.c. of immune blood and 40 c.c. of serum were given intravenously. Two days later the patient was given another 40 c.c. of serum. Then the temperature dropped rapidly to normal, and the convalescence was interrupted only by a transient temperature rise due to retained pus in the incision of the jugular ligation. A blood culture performed fifteen days after admission was negative. The pus secured from the mastoid operations gave a pure growth of hemolytic streptococcus. This child received, in all, 600 c.c. of blood and 200 c.c. of convalescent serum.

This group of cases includes patients in whom the onset of illness was with an acute throat condition, following which one or more of the severe complications of the cervical glands, ears, mastoids, and sinuses developed, with or without an associated positive blood culture. In these patients, repeated massive doses of convalescent serum have been found necessary. Very often there is an associated secondary anemia, and in the presence of anemia whole blood from a recovered scarlet

fever donor is invaluable. The clinical response in these cases is only occasionally striking, but a rather large number of patients on whom reports have been made indicates that persistent massive serum therapy is an important factor in checking the fulminating disease and in ultimate recovery.

III. *Hemolytic Streptococcic Infections of the Surgical Type*

CASE 1.—F. S., aged 23 years. This patient was admitted to the hospital with cellulitis of unknown etiology, affecting both legs, and temperature of 101° F. Heat was applied; the temperature dropped to normal; the patient felt much improved, and abscesses localized on the lower third of the left leg and on the upper half of the right leg. Seven days after admission these abscesses were incised under local anesthesia, with the liberation of thick pus which gave a pure growth of hemolytic streptococcus. Following the incision of the abscesses, the temperature started to climb, and thirty-six hours later there was a marked chill. The following day the temperature rose to 104° F., and the patient was quite toxic and prostrated. In the belief that a septicemia had developed, a blood culture (which gave no growth) was taken and 100 c.c. of convalescent scarlet fever serum was given intravenously. There was a dramatic drop in temperature and a concomitant improvement in the clinical picture. The following day the temperature rose only to 100.2° F., but another 100 c.c. of convalescent serum was given intravenously. Following this, the patient was completely afebrile, symptom free, and made an uneventful convalescence.

CASE 2.—A. R., aged 5 years. This child's clothes caught fire and resulted in extensive second and third degree burns of the chest, back, abdomen, part of the thighs, face, and arms. Tannic acid was applied; heat, sedatives, and fluids were administered.

For several days the child's condition was as good as might be expected. A temperature of 100 to 103° F. persisted, and the course was steadily downhill. Nine days after admission, in the belief that there was a definite cause of the maintained temperature, the tannic acid eschar was removed, and revealed extensive pus accumulation, which gave a pure growth of hemolytic streptococcus. Irrigation of the infected areas was instituted. The following day sulfanilamide was started, and after the child had received 90 grains of the drug, he became quite cyanotic. Since his general condition was unimproved and since two blood cultures were strongly positive for hemolytic streptococcus, 80 c.c. of scarlet fever convalescent serum was given intravenously. The following day the child received 45 grains of sulfanilamide and 200 c.c. of blood. Again cyanosis developed, and the sulfanilamide therapy was stopped. Eighty cubic centimeters of convalescent scarlet fever serum was given intravenously each of the next two days, following which the temperature gradually dropped to a relatively low level, and the blood culture became negative. Although a low grade temperature persisted, the child made a relatively uneventful convalescence.

In this group of cases convalescent serum is inconstant in its effects. At times the response to serum therapy is spectacular. In most instances the response is delayed, and in some cases no effect is observed. It is of paramount importance in these patients that at no time are sound surgical measures to be neglected. The use of serum as stated by Goldberg is not a substitute for, but an adjunct to, sound surgery and other supportive therapy.

Although distinct improvement may be observed in the patient's general condition, arrest of the illness cannot be expected until localized collections of pus are drained. The treatment of these cases with serum is not as specific as could be desired, because at the present time we have no reliable laboratory test to determine action of serum against a given strain of organism. In the absence of this specificity, pooled

serum in massive doses, administered intravenously, gives the greatest hope for success. Immunotransfusion is a supplementary measure that should not be ignored, but it offers less specific value than massive doses of serum.

Convalescent Serum in Whooping Cough

F. M. Meader, M.D.

Experience with the prophylactic use of human convalescent serum against measles and scarlet fever has been so successful that the question has been raised about its value in the prevention of whooping cough. The literature has been reviewed up to 1935 and published by Bradford.[1] His summary cites 58 children chiefly under three years of age given 10 c.c. of serum taken in the eighth week of convalescence, or of from 10 to 20 c.c. of whole blood taken from a parent who had recovered from whooping cough in early life. Forty-four of these children remained in homes where one or more whooping cough patients resided. Twenty-seven received the injection during the incubation period. In 15 the disease developed in a mild form; only one had a complication; the remainder did not develop whooping cough. Twenty children similarly exposed, who did not receive serum, were used as controls. Of this group 8 developed whooping cough in a mild form. Eight had the disease in a moderate degree of severity, and 4 had it in a severe form. Complications developed in 4 children.

In a group of 16 patients exposed outside the home, 9 were given serum during the incubation period. The number completely protected suggested that perhaps they had never been infected. Dr. Bradford concludes that immune blood is probably effective in the prevention and modification of whooping cough if given before catarrhal symptoms appear. If given after the symptoms have begun, favorable results are less apparent.

Our experience in Detroit[2] comprises 94 treated, exposed children of whom 16, or 17 per cent, developed whooping cough, and 154 untreated, exposed children of whom 92, or 60 per cent, developed whooping cough. When these data were adjusted to age distribution, it was found that about 72 per cent of the treated children were apparently protected. In this study we learned how important it is to scrutinize our data carefully. As first compiled, we could find only about 32 per cent protected. Since there were so many variables, we concluded that the serum was of no value as a prophylactic. We discontinued preparation of the serum. But several of our pediatricians insisted that the serum had value and desired another trial. We then reviewed our data and found that we had charged against the serum-treated group several patients who had been given the serum a day or so before they developed the whooping cough. We also found that we had included among the controls several children who developed the disease one or two days after first exposure. Since whooping cough does not develop one or two days after exposure, these should not be included among the controls. When these corrections were made, we were pleased to find that apparently 72 per cent of the treated children had been protected. Dr. Pearl Kendrick[3] and her associates have shown that immunized adults have a potent serum for prophylactic purposes.

The next question of interest is, What change has there been made in the patient or his blood which usually makes him immune from further attacks of whooping cough? Several papers[4] have appeared which show that agglutinins, precipitins, complement fixing bodies, and opsonins are present in the blood of those recovered from the disease, and in the blood of those who have been immunized. These bodies begin to appear about three weeks from onset, increase to a maximum in a few weeks, and then recede to a comparatively small amount in about six months. It is noted that ever after the body seems to respond rapidly to a further increase of antibody should the usual stimulation be forthcoming.

Are all these reactions due to different antibodies, or are these phenomena due to a single antibody which manifests itself in different ways by the different techniques used? In order to rationalize a prophylactic practice for whooping cough and other childhood diseases, suppose we digress for a moment to attempt to visualize the antigen, its antibody and the result of the union of the two. Immunologists have been particularly active in this field of late. Burnet, Keogh, and Lush[5] visualize circulating antibodies as "serum globulin molecules, the surface of which carries one or more specifically modified 'patches.' The arrangement of atoms and the associated electrical fields on such a 'patch' are adapted to unite specifically with one or other 'determinant groups' of the antigen which stimulated the production of the antibody in question." "Antigens are large molecules or aggregates of molecules usually, but not necessarily, composed partly or wholly of protein, and presenting on their free surface a number of 'determinant groups.'"

In stating the principles of active immunization against man's infections, the above authors mention three principles: (1) The use of active virus introduced into the body by such a route that an infection of the tissues produces trivial pathologic changes. (2) Attenuated virus is introduced into the body as in vaccinating against smallpox, and (3) active virus is introduced with an amount of immune serum sufficient to prevent clinical infection. The prophylactic use of measles convalescent serum to contact children is cited. The serum is given about halfway through the incubation period and converts the infection into a mild or abortive one, which, however, provides the child with a subsequent immunity.

For the purpose of this discussion the above mechanism is suggested as a theoretical explanation of the results obtained with whooping cough convalescent serum. While the virus of measles and the Bordet-Gengou bacillus are recognized as different kinds of inciting agents, the principle is conceived to be the same.

If this fundamental conception is correct, two matters are of importance: first, the potency of the serum and second, the stage of the incubation period. At the beginning the number of invading organisms must be relatively few while toward the end of the incubation period they must be very numerous. A given dose of serum sufficient at the beginning of infection might be inadequate during the latter part of the incubation period.

Debré reported[6] the giving in 2 or 3 c.c. amounts pooled blood serum obtained from patients after the fourth week of whooping cough. This serum was given to children under three years of age. He noted that, when it was given early in the incubation period, the children were protected; when given at about the onset of clinical symptoms, the course of the disease was mild; but if given later in the disease, no change was observed. Others have reported a similar experience when using small amounts. Our experience with 7.5 c.c. and 10 c.c. packages would suggest an opportunity to exercise judgment in meeting a given situation. In northern climates during the winter months one would prefer to postpone the disease until a milder climate appears. For this purpose, if the child is young and it is possible to give the serum during the first week after exposure, a small dose, 2 to 5 c.c., should prevent the development of the disease at this time. If the child is over three years of age and/or the period since first exposed is more than seven days, a dose of 10 to 15 c.c. of serum should be given to prevent the clinical symptoms of the disease. If the climate is mild and there are no other extenuating circumstances, the doses and time for giving the serum should be regulated so that the child may develop mild whooping cough in order to secure permanent immunity.

Table I indicates the experience with whooping cough in Detroit as far as we know it since 1920. The reported cases are presented in the first column. The population of Detroit in 1920 was a little under one million. During the past 17

TABLE I

WHOOPING COUGH

DETROIT—1920 THROUGH 1937

YEAR	CASES REPORTED	DEATHS	CASES REPORTED PER 1,000 POPULATION	DEATHS PER 100 CASES REPORTED	DEATH RATE PER 100,000 POPULATION	YEAR	CASES REPORTED	DEATHS	CASES REPORTED PER 1,000 POPULATION	DEATHS PER 100 CASES REPORTED	DEATH RATE PER 100,000 POPULATION	SERUM (C.C.)
1920	2,790	136	2.73	4.9	13.3	1928	5,395	85	3.91	1.6	6.2	2,442
1921	2,691	108	2.86	4.0	11.5	1929	4,100	90	2.87	2.2	6.3	4,985
1922	2,469	89	2.59	3.6	9.3	1930	3,467	46	2.19	1.3	2.9	2,620
1923	2,745	82	2.61	3.0	7.8	1931	5,389	66	3.53	1.2	4.3	6,705
1924	2,062	58	1.82	2.8	5.1	1932	5,922	75	3.97	1.3	5.0	4,975
1925	3,305	87	2.65	2.6	7.0	1933	4,986	44	3.36	0.9	3.0	2,311
1926	3,041	89	2.36	2.9	6.9	1934	4,304	28	2.90	0.7	1.9	0
1927	3,646	61	2.73	1.7	4.6	1935	5,587	42	3.60	0.8	2.7	0
						1936	7,433	41	4.51	0.6	2.5	3,345
						1937	3,352	23	2.02	0.7	1.4	2,255

years, the population has increased about 664,000; therefore the increased number of reported cases may be caused by the increase in population. It will be noted that deaths have steadily decreased during the years. We began to make whooping cough serum available in 1928. This was soon followed by the use of cough plates to aid in diagnosis. The availability of whooping cough vaccine has also improved so that there is a much stronger "whooping cough consciousness" now than formerly. Physicians are being called earlier; opportunity to prevent complications has increased. These changed conditions apparently account for the improvement in the record. The trend curve in the fatality rate indicates a decline of 11.27 per cent per year during the first eight years and a decline of 13.5 per cent during the last ten years. The trend in the death rate per 100,000 population declined 14.4 per cent during the first 8 years and declined 15.1 per cent per year during the last ten years.

Blood serum is obtained at a serum clinic which is held from two to eight times per week, depending upon the need for the various serums. The serums are from persons who have recovered from measles, scarlet fever, whooping cough, mumps, chicken pox, poliomyelitis, and normal individuals. One or two nurses are detailed to watch the released patients having one of these diseases. These nurses contact the patient, offer $10.00 for a sample of blood and, if he accepts, arrange for an appointment at a suitable clinic. These patients have good health and a negative Kahn test and weigh at least 100 pounds. They have recovered from the disease within one year and many return for bleeding at monthly intervals. Ten individuals constitute a clinic.

The blood is drawn into sterile 250 c.c. centrifuge tubes. Specimen is stored in a refrigerator about twenty-four hours. The clear serum is drawn off, and the clot is centrifuged to express more serum. Serums which are reported Kahn negative are pooled, and merthiolate is added to the dilution of 1:10,000. The serum is stored until needed. When required for use, the serum is filtered through an N Berkefeld candle and packaged. Two packages are selected and tested for sterility and toxicity, and two other packages are sent to the laboratory of the state department of health for similar tests. These tests are completed in about seven to ten days. If found satisfactory, the serum is released. Serum which is not to be used at once is dried and stored. However, most of the serum is used as fast as it can be prepared.

The whooping cough serum is used in 12 c.c. doses in hospitals or other institutions where an exposure appears, in order to prevent cross infections. It is recommended and frequently used on young children in homes where a case of whooping cough occurs, provided it can be given during the first week of exposure. The dose is usually the content of a package—12 c.c. The reactions are practically nil. There is no charge for the serum, but the physician may charge for his service in giving the serum.

Our study indicates that, when similar groups of treated and untreated exposed children are compared, about 72 per cent of the suitably treated will not develop whooping cough. The physician who understands the precise use of convalescent whooping cough serum, and has an opportunity to use it skillfully, may expect many happy results. The most favorable effects are observed in children during the first three years of life.

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The Treatment of Active Measles With Human Convalescent Serum

Sidney O. Levinson, M.D., and James A. Conner, M.D.

Whenever the question is raised concerning the treatment of measles with convalescent serum, the common answer is, "There is no value in this therapy after catarrhal symptoms have set in." It is rather difficult to determine the grounds upon which this feeling has been established. Since Weisbecker in 1896 first mentioned the use of convalescent measles serum for therapy, there have been few additions to the literature, which have been sufficiently critical to justify the framing of any opinion. Nevertheless, if an expression is made, it is usually unfavorable.

With few exceptions, the reports in the literature at present deal with the treatment of this disease after the rash has appeared. In the absence of a very large number of cases with a suitable number of controls, any deductions from this type of study would be open to criticism, because of the fact that, after the appearance of the rash, it is customary for the temperature to drop and for symptoms to diminish. In addition, in most instances the serum was administered in relatively small dosage, that is, 5 to 10 c.c., and was given either intramuscularly or subcutaneously.

In this study an attempt was made to secure objective evidence of the effect of serum therapy. In order to achieve this, it was decided that no serum was to be administered until a diagnosis of measles could definitely be made from the clinical symptoms and the presence of Koplik's spots, but before the appearance of the eruption. Since the prophylactic dose for measles is 5 or more cubic centimeters, it was decided that no real therapeutic test of serum could be made unless five to ten times this amount was used for treatment, basing this dosage upon the experience with diphtheria antitoxin. In order to secure as prompt an effect as possible, we attempted to give the serum intravenously, to avoid the delayed absorption following intramuscular or subcutaneous administration. The cases were studied from the viewpoint of the temperature, the character of the exanthem, and the severity of invasive symptoms.

Most of the cases available for study were patients at the Municipal Contagious Disease Hospital of Chicago, who were in the hospital because of some other infectious disease. They developed measles either from an inadvertent exposure in the hospital, or from a previous unsuspected exposure before admission. In the sixteen cases studied in this way, six patients received 20 c.c. of serum; four, 30-40 c.c.; and six, 50 c.c. Eleven patients were suffering from an acute scarlet fever or some septic complication of this disease, while three were convalescing from diphtheria, and one from chicken pox. The development of measles in hospital patients of this type, naturally presaged a stormier course and graver prognosis than one would expect in an uncomplicated case of measles.

Temperature.—Although the temperature curve during the invasive period of measles is not constant or characteristic, there are three common curves, which are seen in most of the cases. Although the maximum temperature may be under 103° F., most children have a maximum between 103 and 105° F., the exception usually occurring in those infants under eight months of age, who still retain a partial maternal immunity. Although the maximum temperature may develop before the eruption, in most instances the maximum temperature is reached after the appearance of the eruption. Abt states:

"The time at which the maximum temperature is reached is dependent, to a certain extent, on the time at which the eruption begins to appear. If this occurs in the morning, the highest point is usually reached at that time, and the remission of the following morning is slight."

The temperature curves of these patients who received serum are quite interesting in view of what may be usually expected. Six patients actually had a normal temperature on the evening of the day the rash appeared. In most cases the temperature fell abruptly following the administration of serum, despite the fact that the rash had not appeared and that these children were suffering from another illness. We have observed that the effect on the temperature is much less evident when the serum is given intramuscularly than intravenously.

Eruption.—The exanthem of measles is a characteristic and recognizable feature of this disease. A description is needless. However, there is a marked change in the exanthem seen in sero-attenuated or modified measles. In the latter form, the eruption is pale, discrete, and the macules may be relatively few, but, even if numerous, they do not tend to coalesce.

In 11 of the 16 patients treated, there was distinct modification of the eruption. Attenuation of the eruption of this kind was seen most commonly when serum was given several days before the eruption appeared. There was little evidence of change in the character of the eruption if the serum was given shortly before the exanthem developed. In one case in which the serum was given into the buttocks, a peculiar effect was observed. In this instance, there appeared to be only a regional serum effect on the rash, of bathing trunk distribution, and might well be called a "regional Debré phenomenon."

General Effect.—Perhaps an even more marked effect of the serum than is reflected in either the temperature or the eruption was the symptomatic response. In practically all instances these children did not behave as if they were developing measles. The most marked effect was probably on the cough, which in most instances was quite mild. The children were not prostrated, many of them sitting up in bed and taking nourishment and food. This alleviation of symptoms was striking in view of past experience with measles developing in sick children in the hospital.

This study was limited to patients in the pre-eruptive stage of measles in whom a definite diagnosis could be made from the characterstic prodromal symptoms and signs. Serum given in this stage had a definite beneficial effect upon the symptoms and frequently caused a modification of the rash; the temperature course in general was lower than ordinarily would be expected even in uncomplicated measles.

No definite determination has yet been made of the proper dose of serum to be used, but it is felt that, early in the catarrhal stage, 20 c.c. is necessary; whereas, later in the catarrhal stage, from 40 to 60 c.c. is required to produce a definite clinical effect. The serum must be given intravenously, in order to derive as prompt action as possible.

It is still a matter of conjecture, and, as stated previously, it will require an extensive study with adequate controls to determine beyond question whether serum is of value after the rash has developed. However, in view of the fact that a definite influence is observed even after the appearance of Koplik's spots, there is good reason to believe that the serum will be of some value even later in the course of the disease. Little benefit can be expected, however, with small doses of serum. Since 20 to 40 c.c. of convalescent serum is required to produce an effect late in the catarrhal stage, one would anticipate that a larger dose, perhaps 80 or 100 c.c., would be necessary later in the disease.

Because of the massive doses that are required, it is obvious that treatment of measles will necessarily have to be limited to selected cases. Whereas the prophylaxis of measles may be practiced generally because of the small dose required for prevention, treatment will have to be limited to those children in whom the development of measles would offer a grave prognosis.

DR. HYLAND.—We have added one report of observations, not previously listed.

Failures After Immunization With Scarlet Fever Serum

E. S. Platou, M.D., and Paul F. Dwan, M.D.
Minneapolis, Minn.

Most observers who have reported on the prophylactic merits of convalescent serum contrast the incidence of the subsequent scarlet fever complex with the average morbidity among unprotected contacts. If these doses of serum modify the complex to the extent of preventing or modifying the rash, may it be that erroneous conclusions with respect to bacterial invasion might result? Can we be sure that fewer cases of invasion actually occur especially if there has been no previous appraisal of host resistance? A recent experience of one of us with intimately exposed individuals makes us wonder whether inadequacy of dosage or the quality of a given pool might account for frank failures such as occurred in five of ten children (ages 12 to 16 years) each of whom received convalescent serum.

One of a group of eleven English choir boys touring this country contracted scarlet fever while in Chicago. He was immediately removed to the municipal contagious hospital, and the ten remaining boys were given 20 c.c. of pooled convalescent scarlet fever serum. The subsequent course of these cases seems interesting enough to warrant detailed description.

After seven days of isolation, the ten boys were permitted to proceed to Madison, Wis., where on the eighth day after receiving serum, J. C. (Case 1) was sent to a hospital with scarlet fever. On arriving in Minneapolis, ten days after serum administration, G. P. (Case 2) was taken severely ill with angina, hyperpyrexia and prostration. Because throat cultures showed the presence of hemolytic streptococci, he was quarantined in the Minneapolis General Hospital. A very faint erythema appeared in his axillae at the end of forty-eight hours. During his stay in this hospital, the boy developed otitis media, cervical adenitis, a mild nephritis and desquamation.

The day following G. P.'s admission to the hospital (eleven days after serum administration), A. C. (Case 3), who gave a history of sore throat and fever three days after serum administration, had a typical postscarlet tongue, slight desquamation, and remained culture positive during three weeks of quarantine. This boy gave no history of previous scarlet fever and is now Dick negative. K. S. (Case 4), developed sore throat and fever the same day that A. C. (Case 3) was isolated, but recovered promptly without developing a rash or complications and was released under observation with two negative cultures at the end of one week.

J. S. (Case 5), was taken ill with sore throat and had a positive culture the same day as K. S. (Case 4) and although he developed no rash, his tongue gradually assumed a strawberry appearance, his temperature rose intermittently to 105° F., and he developed pyelonephritis, renal abscess, multiple arthritis, and endocarditis.

The remaining five boys received sulfanilamide in addition to their seroprophylaxis, beginning immediately after J. S. (Case 5) became sick, and developed no symptoms.

Prophylactic doses of commercial antitoxin have likewise been found lacking in adequate protection against bacterial invasion. During the past several years there have been admitted to the Minneapolis General Hospital five patients with serious cases of scarlet fever who have been *known* to have had such prophylaxis two to twelve days previously. Two of these patients died, one from streptococcic laryngotracheobronchitis and the other from septicemia.

The striking results that we have seen in treating septic scarlet fever with serum and sulfanilamide have led us to speculate on the possibilities of combined sero- and chemoprophylaxis.

DISCUSSION

DR. M. A. F. HARDGROVE (MILWAUKEE, WIS.).—The Milwaukee Serum Center, in existence three years, was stimulated by Dr. Thalhimer. It is operated on a nonprofit basis, in a small community hospital. The serum is obtained by bleeding patients and is prepared as Dr. Meader described. We have found it very satisfactory in the treatment of scarlet fever.

In patients exposed to measles, I believe we need some correction in dosage or in the date of administration after the child has been exposed. We have found a satisfactory improvement in the complications of measles by use of convalescent scarlet fever serum. We have not treated patients who have already developed measles.

In mumps, we have had only limited experience. Complicated mumps seems to be helped, orchitis greatly benefited.

The use of convalescent whooping cough serum during the active stage has not seemed to help.

DR. THALHIMER.—How much serum did you use?

DR. HARDGROVE.—In two cases we used a single large dose of 40 c.c. In the other cases, 20 c.c. twice a week.

DR. PLATOU.—I wish to thank all of you for the courtesy shown Dr. Evelyn Johnson of our laboratory in her recent tour of the country.

In regard to scarlet fever it seems to me that no discussion is complete without mention of sulfanilamide therapy. We have just analyzed 200 cases, in 100 of whom sulfanilamide was used in the doses recommended by Long and Bliss. The rate of recovery from the toxic phase of the disease was no more rapid in the treated than in the controls (six days). However in the untreated cases there were 41 complications, 9 of which were suppurative; whereas only 8 complications, one of which was suppurative, occurred in the treated cases.

The most striking of the treated cases was a parturient woman with multiple skin abscesses from which pure cultures of hemolytic streptococcus were recovered. This woman recovered.

The possibility of a synergistic effect of the drug with serum should be investigated further. The combination of the two seems to me the best method of attack against scarlet fever.

DR. THALHIMER.—I have some more material here. Dr. Bullowa has used large repeated doses of convalescent scarlet fever serum in 13 cases of proved *Streptococcus hemolyticus* pneumonia. Only one patient died. Sulfanilamide was given also in maximum doses in some. In some it had to be discontinued because of toxic symptoms. Those receiving only serum recovered just as well as those with combined therapy. This is very careful work with carefully observed results.

It seems possible that there is a synergistic action of sulfanilamide and convalescent serum, but we will have to go farther and get a base line for each before this can be studied.

Dr. Conner's paper interested me. We have been able for two years to mitigate measles in the Koplik-spot stage. Dr. Kohn, Dr. Klein, and Dr. Schwarz have treated 24 children at Willard Parker Hospital. They found unquestionable modification in 19, questionable in 1, and no effect in the other 4. In most cases, 50 c.c. of measles convalescent serum was given intravenously, in a few 40 c.c.

intravenously, and then more serum intramuscularly. They started believing that really large doses should be given. Later, if it was effective, the dose could be reduced.

Injection of convalescent serum on successive days seems to cause a delay in the appearance of the rash until the injections ceased.

Fifty cubic centimeters of normal human serum was given to six or eight children without any beneficial effect. Then we decided to give amounts of normal serum comparable in measles prophylactic effect, i. e., four times as much as would be given of convalescent serum or about 200 c.c. Because of the large amount, we used serum which was concentrated to one-third in cellophane bags. There was definite modification of the measles in one case of four, possible in the second, and none in the other two. I think this type of therapy valuable in the pre-eruptive stage in debilitated children or in children with other diseases.

DR. LEVINSON.—Dr. Conner's cases were observed in the hospital. In private patients, also, we find serum valuable in the pre-eruptive stage. In the eruptive stage the response is manifested by a drop in temperature and decrease in toxicity, not in the change in rash. The therapeutic dose is small early in the catarrhal stage and must be increased as the disease progresses. Twenty cubic centimeters of serum is sufficient before or when the Koplik spots show, while just before eruption 50 c.c. is necessary. This is comparable to the experience in the prophylactic administration of measles serum.

DR. THALHIMER.—Dr. Platou has shown the safety and excellency of peritoneal administration of serum.

DR. H. A. TOWSLEY (ANN ARBOR, MICH.).—With regard to sulfanilamide therapy of scarlet fever in 50 cases, we have tried to keep the blood concentration of the drug between 9 and 15 mg. per cent. At the end of two weeks many of these patients still had positive beta hemolytic streptococcus throat cultures.

I would like to ask the value of blood transfusion in whooping cough.

DR. CONNER.—Blood transfusion from adult donors is definitely of value in severe cases of whooping cough in infants under one year.

DR. PLATOU.—The work of Dr. Conner, Dr. Levinson, and Dr. Thalhimer is very interesting and opens up a field we have regarded as almost useless. The dosage and time of administration are important. This is a real contribution.

DR. TOWSLEY.—What is the comparative value of placental extract and convalescent serum in measles?

DR. THALHIMER.—We have not used placental extract. But the globulin fraction of normal human serum, as described by Karelitz, is just as effective, but not more so, than convalescent serum.

DR. CONNER.—At the present time I do not have a complete analysis of our cases. In Chicago during the past six months we have had a high incidence of measles. Cases have developed in the corridors of the hospital. Spread of measles is possible through the corridor but not likely to different corridors. We have used in the various corridors, convalescent serum, normal human serum, and placental extract. My impression is that convalescent serum is the most effective, normal human serum in doses of 40 c.c. next, and placental extract least effective. Local and general reactions are frequently seen when placental extract is administered.

DR. TOWSLEY.—We have recently used cord blood serum obtained at the time of delivery in 10 c.c. doses and have felt it was quite effective in the prophylaxis of measles. Of 15 patients, 3 developed mild symptoms of the disease, after a continuous exposure in the home.

CHAIRMAN HYLAND.—I was interested in what Dr. Hardgrove said about serum modifying whooping cough. A young pediatrician of my acquaintance has treated 12 or 15 cases with serum intravenously and thinks the whooping cough greatly modified.

As to diverse streptococcal infections, I have seen many of these. A girl clawed by a lion, with a severe purulent infection, temperature 106° F., blood culture positive, was treated with scarlet fever serum and was discharged cured in six days. Two other patients with very severe streptococcus infections recovered after intravenous convalescent serum. I have seen other cases.

I have also seen dramatic recovery in one case of streptococcus pneumonia after 100 c.c. of scarlet fever serum.

Dr. Meader, did you have good results with adult human serum?

Dr. Thalhimer, what was the antistreptolysin content of the serum you used?

DR. MEADER.—Dr. Pearl Kendrick reported that the immunizing of normal adults with pertussis vaccine produced a means of obtaining serum satisfactory for use in the prophylaxis of whooping cough.

DR. H. F. GARRISON (JACKSON, MISS.).—How long can serum be kept sterile? When should convalescent serum be taken?

CHAIRMAN HYLAND.—I presume it can be kept sterile indefinitely. Measles convalescent serum is taken from the seventh day of the disease to the end of the second month, scarlet fever serum from the twenty-first day to the end of the sixth month. We are not allowed to take it after the end of the sixth month if operating under a license granted by the National Institute of Health.

DR. CONNER.—In 1935 our results in measles were much more striking and the clinical results in all ways more definite than this year. This year the Koplik spots appeared very late or not at all; consequently serum was given late in the course of the prodromal symptoms. The temperature response was not as marked as previously, but clinically there was great improvement following the administration of the serum. This improvement is of vast importance especially in children in poor physical condition and in contagious disease hospitals. I believe we have something of value.

DR. MEADER.—Explain the Schultz-Charlton test to me.

DR. THALHIMER.—One c.c. of convalescent serum is injected intradermally and with a scarlet fever rash there is definite blanching of the skin in this area. At Willard Parker Hospital they have been using in all patients, as well, 1 c.c. of 1 to 100 dilution of antitoxin intradermally. There is more definite blanching in a larger number of cases of scarlet fever with the convalescent serum test than with the antitoxin.

CHAIRMAN HYLAND.—At the last meeting of Group IV, Dr. Paul Hamilton reported on the complications of scarlet fever at the Los Angeles General Hospital. Previous to two years ago, complications occurred in 42 per cent of cases. In a series treated with convalescent serum, complications were 8 per cent.

DR. R. G. SHARP (SAN DIEGO).—May whole blood be used when serum is not available?

DR. LEVINSON.—Intravenous administration of serum for treatment is the method of choice. This was not stressed by Dr. Thalhimer, probably because of lack of time (obliged to leave early). Serum is frequently given in the home where proper preparation of syringe and serum is not always carried out. The syringe boiled in tap water is left with a coating which may be pyrogenic in character. The serum may not be warmed or it may be overheated. The following rules should be observed: (1) Syringe should be sterilized in an autoclave after washing with distilled water; (2) serum should be warmed to 70° F.; (3) slow administration. Take fifteen to thirty minutes to give 100 c.c.

For prophylactic use, the serum is preferably given intramuscularly or subcutaneously, because delayed absorption is desired. The resultant passive immunity is temporary and depends on the rate of elimination of the serum from the body. If the exposure to infection is prolonged, the serum should be repeated in ten to fourteen days to maintain a high titer of passive immunity in the body.

DR. MEADER.—Was the measles serum titrated to determine any possible value against streptococci?

DR. CONNER.—In giving the measles serum, a small amount was injected intracutaneously on withdrawing the needle from the vein. Blanching occurred in this cutaneous area when the rash appeared. Our work on serum treatment of measles was undertaken because some of the doctors who secured serum for prophylaxis used it instead for treatment and reported favorably on such use.

Our recommended dose has varied from that time for two reasons: (1) availability, and (2) to determine effect of various amounts. It was found that 50 c.c. was of more value than 25 or 30 c.c.

Measles superimposed on scarlet fever adds greatly to the patient's hazard. Since using convalescent serum, none of our patients have been lost.

DR. L. J. SCHERMERHORN (GRAND RAPIDS, MICH.).—Do you use serum in all your scarlet fever cases?

DR. CONNER.—No, but all critical cases do receive it.

DR. SCHERMERHORN.—What is the dosage?

DR. CONNER.—From 20 c.c. to 200 c.c. is given. We plan to give all that will be needed, in the first dose.

DR. LEVINSON.—The measles serum was not titrated to determine its value against streptococci.

DR. SHARP.—What is the value of transfusion as compared with serum?

DR. CONNER.—Immune transfusion is rarely used when serum is available.

CHAIRMAN HYLAND.—This concludes the discussion. Although the number attending this Round Table has been rather small, I think the discussion has been most interesting and valuable.

RUTH MORRIS BAKWIN, Secretary.

Academy News

The following appointments have been made for the Program Committee of the Academy: Chairman, Dr. Edgar E. Martmer (3 years); Dr. Irvine McQuarrie (1 year); and Dr. Philip Van Ingen (2 years).

Dr. W. A. Shaw of Reno, Nevada, died Jan. 21, 1939.

Dr. Joseph C. Palmer, of Syracuse, N. Y., died October 7, 1938.

Dr. Lucy Porter Sutton, of New York City, died on Friday, December 23, of acute leucemia. Dr. Sutton had been an active worker in pediatrics for many years and was instructor in diseases of children at the College of Physicians and Surgeons, Columbia University.

Dr. John K. Bullock of Jackson, Mississippi, died during the last week of December, 1938.

Dr. T. Wingate Todd, an Associate Fellow of the Academy, died Dec. 28, 1938, at Cleveland. Dr. Todd was Professor of Anatomy at Western Reserve and Director of the Brush Foundation. His studies on bone growth made him an international figure. He became closely associated with the pediatric group through the Third White House Conference, in which he took an active part, and was made an Associate Fellow when the Academy was organized.

Dr. Ward E. Collins, of Kalamazoo, Mich., died on Dec. 31, 1938. Dr. Collins was the pioneer in pediatrics in Kalamazoo. He was graduated by the University of Michigan in 1908 and took his training in pediatrics in the University of Minnesota. During the War he served in the army over seas.

News and Notes

Dr. Percival J. Eaton died Dec. 28, 1938, at the age of 76 years. Dr. Eaton was one of the early pioneer specialists in pediatrics in America. He practiced in Pittsburgh, Pa., from 1890 until his retirement, which took place a few years before the Academy was organized.

The following physicians have been certified by the American Board of Pediatrics since the last report:

Dr. Abraham Edwin Bernstein, Staten Island, N. Y.
Dr. Harry Edwin Blair, Hagerstown, Md.
Dr. Harry D. Bowman, Hagerstown, Md.
Dr. Abe S. Brown, Waterbury, Conn.
Dr. Thos. S. Bumbalo, Buffalo, N. Y.
Dr. Arthur J. Cramer, Jr., Kenmore, N. Y.
Dr. Robert Day Mortimer Cunningham, Stamford, Conn.
Dr. Belle Dale, Port Washington, N. Y.
Dr. Hyman Peter Fine, Perth Amboy, N. J.
Dr. Stanley S. Freedman, Providence, R. I.
Dr. Daniel Foster Harvey, Hartford, Conn.
Dr. Theodore G. Holzsager, Brooklyn, N. Y.
Dr. Albert L. Lewin, Medina, N. Y.
Dr. Merritt Burnham Low, Greenfield, Mass.
Dr. Alex. S. Manne, Brooklyn, N. Y.
Dr. Aims Chamberlain McGuinness, Philadelphia, Pa.
Dr. Alfred A. Nathans, Brooklyn, N. Y.
Dr. Thomas Eugene Shaffer, Farmington, Conn.
Dr. Harry Sherman, Brooklyn, N. Y.
Dr. Jacob Wallace, Boston, Mass.

Dr. Ben Andres, Longview, Texas
Dr. Robert M. Finks, San Angelo, Texas
Dr. Amos Carvel Gipson, Gadsden, Ala.
Dr. Ernest L. Glasscock, Kansas City, Mo.
Dr. Guy L. Hacker, Dallas, Texas.
Dr. Jerome Sylvan Harris, Durham, N. C.
Dr. Byron Arthur Jenkins, Lubbock, Texas.
Dr. George S. Littell, Dallas, Texas
Dr. Frank McPherson Martin, San Antonio, Texas.
Dr. Bernard A. Mazur, Fargo, N. D.
Dr. Earl G. Padfield, Salina, Kan.
Dr. Charles J. Stettheimer, Denver, Colo.
Dr. William Edgar Van Order, Chattanooga, Tenn.
Dr. Sidney S. Weinstein, Denver, Colo.
Dr. Stanley George Wolfe, Shreveport, La.

Book Reviews

A Handbook of Methods for the Study of Adolescent Children. By WILLIAM WALTER GREULICH, PH.D., HARRY G. DAY, SC.D., SANDER E. LACHMAN, M.D., JOHN B. WOLFE, PH.D., AND FRANK K. SHUTTLEWORTH, PH.D. Monographs of the Society for Research in Child Development, Volume III, No. 2 (Serial No. 15). Pp. 406. Washington, D. C.: Society for Research in Child Development, National Research Council, 1938. Price, $2.25.

The Adolescent Period: A Graphic and Pictorial Atlas. By FRANK K. SHUTTLEWORTH, Institute of Human Relations, Yale University, New Haven, Conn. Monographs of the Society for Research in Child Development, Volume III, No. 3 (Serial No. 16). Pp. 246. Washington, D. C.: Society for Research in Child Development, National Research Council, 1938. Price, $2.

These two volumes are complementary. The handbook is intended as a methodological guide to those interested in the study of child growth and development. Each author is responsible for a certain field reflecting his own interests. Greulich contributes chapters on anatomical aspects (including anthropometry); Day, chapters on biologic and physiologic aspects; Lachman covers medical and clinical aspects; Wolfe, the psychologic, and Shuttleworth, chapters on problems of environment and heredity. The methods are fully discussed, and a complete bibliography for each subsection makes the work of extreme value to the worker in these fields.

To the average reader and to the teacher of pediatrics the atlas is of much more value and interest. Shuttleworth has compiled a remarkable collection of graphs and pictures covering practically every phase of adolescence—physical, economic and social problems, and psychologic. It is a reference book that should be available to every student and teacher in the field of childhood.